A prospective observational study to investigate the effect of prehospital airway management strategies on mortality and morbidity of patients who experience return of spontaneous circulation post cardiac arrest and are transferred directly to regional Heart Attack Centres by the Ambulance Service

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Abstract

Introduction

The most appropriate airway management technique for use by paramedics in out-of-hospital cardiac arrest is yet to be determined and evidence relating to the influence of airway management strategy on outcome remains equivocal. In cases where return of spontaneous circulation (ROSC) occurs following out-of-hospital cardiac arrest, patients may undergo direct transfer to a specialist heart attack centre (HAC) where the post resuscitation 12 lead ECG demonstrates evidence of ST elevation myocardial infarction. To date, no studies have investigated the role of airway management strategy on outcomes in this sub-set of patients. The AMICABLE (Airway Management In Cardiac Arrest, Basic, Laryngeal mask airway, Endotracheal intubation) study therefore sought to investigate the influence of prehospital airway management strategy on outcomes in patients transferred by the ambulance service directly to a HAC post ROSC.

Methods

Adults with ROSC post out-of-hospital cardiac arrest who met local criteria for transfer to a HAC were identified prospectively. Ambulance records were reviewed to determine prehospital airway management approach and collect physiological and demographic data. HAC notes were obtained to determine in-hospital course and quantify neurological outcome via the Cerebral Performance Category (CPC) scale. Neurologically intact survivors were contacted post discharge to assess quality of life via the SF-36 health survey. Statistical analyses were performed via Chi-square, Mann Whitney U test, odds ratios, and binomial logistic regression.

Results

A total of 220 patients were recruited between August 2013 and August 2014, with complete outcome data available for 209. The age of patients ranged from 22-96 years and 71.3% were male (n=149). Airway management was undertaken using a supraglottic airway (SGA) in 72.7% of cases (n=152) with the remainder undergoing endotracheal intubation (ETI). There was no significant difference in the proportion of patients with good neurological outcome (CPC 1&2) between the SGA and ETI groups (p=.286). Similarly, binomial logistic regression incorporating factors known to influence outcome demonstrated no significant difference between the SGA and ETI groups (Adjusted OR 0.725, 95% CI 0.337-1.561). Clinical and demographic variables associated with good neurological outcome included the presence of a shockable rhythm (p<.001), exposure to angiography (p<.001), younger age (p<.001) and shorter time to ROSC (p<.001). Due to an inadequate response rate (25.4%, n=15) analysis of SF36 data was limited to descriptive statistics.

Limitations

The study only included patients who achieved ROSC and met the criteria for direct transfer to a HAC. Results are therefore not generalisable to more heterogenous resuscitation populations. Accuracy of clinical decision making and ECG interpretation were not assessed and therefore some patients included in the study may have been inappropriately transferred to a HAC. The low SF-36 survey response rate limited the level of neurological outcome analysis that could be undertaken.

Conclusion

In this study, there was no significant difference in the proportion of good neurological outcomes in patients managed with SGA versus ETI during cardiac arrest. Further research incorporating randomised controlled trials is required to provide more definitive evidence in relation to the optimal airway management strategy in out-of-hospital cardiac arrest.

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Glossary of Terms

ACS	Acute Coronary Syndrome
AED	Automated External Defibrillator
ALS	Advanced Life Support
ANOVA	Analysis of Variance
BLS	Basic Life Support
BVM	Bag-Valve-Mask
CARES	Cardiac Arrest Registry to Enhance Survival
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CPC	Cerebral Performance Category
CPR	Cardiopulmonary Resuscitation
ECG	Electrocardiogram or Electrocardiograph
ED	Emergency Department
ELST	Emergency Life Support Technician
EMS	Emergency Medical Services
EMT	Emergency Medical Technician
$ETCO_2$	End Tidal Carbon Dioxide
ETI	Endotracheal Intubation
ETT	Endotracheal Tube
GCS	Glasgow Coma Score
GP	General Practitioner
HAC	Heart Attack Centre
HR	Hazard Ratio
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
I-LMA	Intubating Laryngeal Mask Airway
INTCAR	International Cardiac Arrest Registry
IPPV	Intermittent Positive Pressure Ventilation
IQR	Inter-quartile Range
LAS	London Ambulance Service
LBBB	Left Bundle Branch Block
LMA	Laryngeal Mask Airway
MI	Myocardial Infarction
mRS	Modified Rankin Scale
MTH	Mild-Therapeutic Hypothermia
NHS	National Health Service
NRES	National Research Ethics Service
OHCA	Out-of-Hospital Cardiac Arrest
OPALS	Ontario Prehospital Advanced Life Support
OR	Odds Ratio
PEA	Pulseless Electrical Activity
PCI	Percutaneous Coronary Intervention
PPCI	Primary Percutaneous Coronary Intervention

PRF	Patient Report Form
PTSD	Post-Traumatic Stress Disorder
RCT	Randomised Controlled Trial
ROC	Resuscitation Outcomes Consortium
ROSC	Return of Spontaneous Circulation
RR	Relative Risk
RSI	Rapid Sequence Induction or Intubation
SF36	36-Item Short Form Survey
SGA	Supraglottic Airway
STEMI	ST Elevation Myocardial Infarction
UK	United Kingdom
USA	United States of America
VACAR	Victorian Ambulance Cardiac Arrest Registry
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1. Introduction

1.1 Background and rationale

Prehospital airway management has a profound effect on mortality and morbidity, and is a fundamental part of routine paramedic practice (Wang & Yealy, 2005, 2006b, 2006a). Historically, endotracheal intubation (ETI) has been the cornerstone of invasive airway management by paramedics (Woollard & Furber, 2010). This involves the passage of a cuffed tube into the trachea under direct laryngoscopy, thus providing protection from aspiration of gastric contents and facilitating asynchronous intermittent positive pressure ventilation (IPPV) in the context of continuous chest compressions as part of cardiopulmonary resuscitation (CPR) (Soar, Perkins, & Nolan, 2013). However, recent research has questioned the value of this technique when performed by practitioners with comparatively less extensive training than physicians and relatively limited procedural exposure (Deakin, Clarke, et al., 2010). Paramedic ETI has been associated with poor procedural success rates, unacceptably high complication rates, and increases in mortality and morbidity (Wang & Yealy, 2005) .

The emergence of alternative supraglottic airway (SGA) devices, such as the laryngeal mask airway and i-gel, has led to calls for the withdrawal of paramedic ETI in cardiac arrest in favour of novel devices, which may constitute acceptable alternatives without the attendant risks and complications associated with ETI (Deakin, Clarke, et al., 2010). Most supraglottic as opposed to extraglottic airways consist of a tube with an elliptically-shaped cuff at the distal end, which may require inflation prior to delivery of IPPV. Insertion of an SGA is perceived to be a less technically demanding procedure which carries a lower risk of malpositioning and may result in less interruptions to chest compressions. Potential pitfalls include the inability to provide asynchronous IPPV and an ongoing aspiration risk due to the absence of a cuffed tube within the trachea (Soar et al., 2013).

Evidence relating to the optimal airway management strategy in cardiac arrest remains equivocal. Many studies report procedural success rates and complications associated with specific devices, but do not address outcomes. Some investigators report improved survival where ETI is performed by paramedics in cardiac arrest (McMullan et al., 2014), whereas others have observed increased mortality (Arslan Hanif, Kaji, & Niemann, 2010). Other research suggests that the aetiology of the cardiac arrest (Takei, Enami, Yachida, Ohta, & Inaba, 2010) or the sequencing of the procedure with other resuscitation tasks may be important factors in predicting the therapeutic value of ETI over other airway management approaches (Turgulov, Rac, Kierzek, & Morrison, 2011).

More recent research has addressed the care of patients who achieve return of spontaneous circulation (ROSC) after prehospital cardiac arrest. Specialist regional centres capable of performing

early angiography and primary percutaneous coronary intervention in patients with sustained ROSC have been established, with some evidence of improved outcomes (Dumas et al., 2010). The establishment of such regionalised systems of care has often been at the expense of longer prehospital transfer times, placing additional demands on paramedics responsible for this phase of care (Cudnik et al., 2010). The effects of inadequate prehospital airway management and inappropriate ventilation strategies on outcomes in certain patients are well documented (Bobrow & Ewy, 2009). To date, no studies have evaluated the influence of prehospital airway management strategies on outcomes in cardiac arrest patients who achieve ROSC and undergo direct transfer to a specialist regional Heart Attack Centre (HAC) for post resuscitation care. This prospective observational study therefore investigates the influence of airway management strategy on outcomes in patients with ROSC undergoing transfer to a specialist HAC after resuscitation by paramedics and other ambulance clinicians following out-of-hospital cardiac arrest.

1.2 Structure of the thesis

At the outset, the thesis defines the research question and associated aim and objectives before progressing to a review of studies relevant to prehospital airway management and literature relating to factors influencing outcome in out-of-hospital cardiac arrest. These are intentionally presented as two distinct sections, with the former establishing a comprehensive and in-depth review of prehospital airway management against which study findings may be bench-marked and the latter providing an overview of the range of factors influencing survival to inform both study design and subsequent discussion of results.

The methodology section describes the study setting and provides a rationale for the chosen methodological approach, drawing on the evidence considered in the preceding literature review. Consideration is given to a range of outcome measures and justification for the chosen measures provided in the context of the methodological approach. The study data collection procedure is detailed and a rationale for the study sample size and approach to statistical analysis provided. This section also discusses ethical considerations and provides details of the requisite mandatory approvals for NHS research.

Results from statistical analysis are then presented in a stepwise fashion, progressing from descriptive statistics defining characteristics of the study sample to comparisons of key demographic and clinical data stratified by factors such as airway management approach and neurological outcome. Latterly, odds of good versus poor outcome based on airway management approach are presented. In the second phase of this analysis, adjusted odds of good versus poor outcome stratified by airway management approach are presented, based on the results of binomial logistic

regression models incorporating factors known to affect survival. Finally, findings from more sophisticated measures of outcome in neurologically intact survivors are considered.

The subsequent discussion of results considers the study findings in the context of national and international out-of-hospital resuscitation and airway management literature. Consideration is given to sample demographics, clinical characteristics and the study setting, comparing and contrasting these with the approach taken in other airway management studies. The significance of potentially confounding factors known to influence outcome is also discussed, drawing on themes emerging from the preceding literature review. Following this, relevant study limitations are acknowledged alongside the associated strengths of and unique contribution made by this work. The thesis concludes by summarising and providing commentary on the significance of the study findings and implications for future practice.

2. Aim and objectives

2.1 Research question

What is the influence of prehospital airway management on physiology, mortality and neurological outcomes in patients who experience return of spontaneous circulation post cardiac arrest and undergo direct transfer by the ambulance service to regional Heart Attack Centres?

2.2 Aim

To examine the effect of different airway management strategies on outcomes in patients who suffer out-of-hospital cardiac arrest and, after treatment by the ambulance service, regain a pulse and undergo direct transfer to a specialist Heart Attack Centre.

2.3 Objectives

- To investigate clinical and demographic variables that may influence outcome
- To investigate the hospital course including clinical management and final neurological and mortality outcomes for this cohort.
- To investigate any variation in physiological data (such as heart rate) between patients treated using different airway management techniques
- To investigate the type of airway management approach employed in relation to patient demographics (such as age or gender).

3. Review of airway management literature

3.1 Introduction

Airway management in out-of-hospital cardiac arrest is a fundamental component of resuscitation (Deakin, Nolan, et al., 2010; Soar et al., 2015) and is provided by a variety of practitioners operating within a range of Emergency Medical Services (EMS) systems internationally (Lockey, 2009). Within the UK, advanced airway management encompassing endotracheal intubation (ETI) and more recently supraglottic airway insertion has been provided by appropriately trained paramedics and other ambulance staff for decades (Briggs et al., 1976; Lewis et al., 1993). This section reviews relevant national and international literature relating to out-of-hospital airway management in cardiac arrest, specifically in relation to procedural success rates for endotracheal intubation, factors influencing success, the influence of airway management strategy on survival, education and exposure of practitioners, procedural complications, and the role of alternative supraglottic and extraglottic devices. Finally, the results from relevant meta-analyses are summarised.

3.2 Paramedic intubation success rates – retrospective studies

Given the methodological and logistical challenges associated with prospective clinical trials of prehospital airway management, an appreciable proportion of studies investigating paramedic endotracheal intubation are of a retrospective nature (Wang, Balasubramani, Cook, Lave, & Yealy, 2010) giving rise to concerns regarding the reliability and validity of data not primarily collected for research purposes (Peat, 2002). Two successive studies utilised retrospective chart review to investigate endotracheal intubation success rates amongst paramedics in the Ottawa region of Canada (Rocca, Crosby, Maloney, & Bryson, 2000; Tam et al., 2009). The Ottawa-Carleton paramedic programme was initially developed with 12 paramedics in July 1995, and by April 1998 had trained and certified a total of 46 paramedics authorised to perform both oral intubation without pharmacological adjuncts and nasal tracheal intubation facilitated by topical anaesthetic and vasoconstrictors. Prior to this, prehospital care was limited solely to basic life support measures, and therefore these studies provide an opportunity to assess development of paramedic airway management in a newly established advanced life support system over time.

In the first study, Rocca et al. retrieved ambulance call reports between January and December 1997 for all incidents in which paramedics documented that airway management was attempted or indicated to establish whether attempts were made to perform endotracheal intubation and the outcome of these attempts (Rocca et al., 2000). The authors defined success as placement of a tracheal tube determined clinically to be in an endotracheal position through which ventilation could be provided, although the methods through which paramedics confirmed endotracheal placement

are not described. During the study period, the 46 intubation-trained paramedics responded to in excess of 12,000 calls, of which 453 had documented evidence of endotracheal intubation attempts. A total of 331 (73%) of these were for patients in cardiac arrest from a range of medical and trauma aetiologies. A further 101 (22%) patients had non-traumatic serious medical conditions and the remaining 21 (5%) had sustained serious injuries.

Paramedics attempted to intubate 385 (85%) patients orally and 68 (15%) nasally. The overall success rate for paramedic endotracheal intubation was 90.1% (n=408). Overall success in the setting of cardiac arrest was 96% (n=318), whereas success rates for patients with serious medical conditions and traumatic injuries were 74.3% (n=75) and 71.4% (n=15) respectively (p<.0001). When data from the medical and trauma groups were combined and compared with the cardiac arrest cohort, the relative risk of intubation failure in the combined medical and trauma group was 3.2 (95% CI 2.5-4.2). Nasotracheal intubation was attempted in 68 patients within the medical and trauma groups, yielding a success rate of 63% (n=43). The rate of successful nasal intubations was lower than that achieved both when oral intubation was attempted across all patient groups (n=365, 94%, p<.001) and in the combined medical and trauma group (n=47, 87%, p<.05). Intubation success rates remained comparatively higher in the cardiac arrest group when nasotracheal attempts were excluded from analysis (96% versus 87%, p=.015).

In 2009, Tam et al. published results from a further retrospective review of prehospital airway management by Ottawa paramedics between July 2003 and July 2005 (Tam et al., 2009). By this stage, 150 paramedics able to provide oral and nasal endotracheal intubation were responding to over 100,000 calls annually. In contrast to the previous Ottawa study (Rocca et al., 2000), these paramedics also inserted laryngeal mask airways in some cases. Data extraction methods were broadly similar, although Tam et al. utilised two independent paramedics to perform chart reviews and collected additional clinical data relating to patient demographics, Glasgow Coma Score (GCS), and call location. Separate definitions were developed for endotracheal intubation via the oral (direct laryngoscopy, accompanied by the insertion of an endotracheal tube past the oropharynx) and nasal (insertion of an endotracheal tube past the nasopharynx) routes. Details of the protocol used by paramedics to confirm endotracheal intubation, which included use of capnometry, were also provided. On the basis of the endotracheal intubation success rates quoted previously (Rocca et al., 2000), Tam et al. estimated that a sample size of 1,000 would provide a 95% confidence interval of ±4% around an anticipated success rate of 90%.

During the study period, 150 paramedics performed advanced airway procedures on 1,063 patients, of whom 1,029 underwent endotracheal intubation. Cases where a laryngeal mask airway was used

as a primary airway (n=34) were excluded from further analysis. The majority of patients were adult (98.4%) and male (62.2%) and had a mean age of 65.5 years (range 0-97 years), with children accounting for 1.6% of all intubations. Oral and nasal endotracheal intubation were performed in 877 (85.3%) and 151 (14.7%) of patients respectively. Oral endotracheal intubation was successful on first attempt in a significantly greater number of cases than nasal endotracheal intubation (66.3% versus 54.9%, RR 1.21, 95% CI 1.04-1.40, p<.05). There were 181 failed intubation attempts managed with a range of alternative approaches, including bag-valve-mask ventilation (n=72), laryngeal mask airway (n=57) and other devices not specifically identified (n=12). Malpositioned endotracheal tubes were identified and repositioned during transport in 15 cases. One endotracheal tube was identified as 'incorrectly positioned' in the Emergency Department, although it is unclear if this was an unrecognised oesophageal intubation. Overall intubation success was 82.7% in this study, which was significantly lower (p<.001) than the 90.7% reported previously (Rocca et al., 2000). In keeping with results reported by Rocca et al., endotracheal intubation was most successful in cardiac arrest patients (86.3%), followed by medical (82.6%) and trauma (69.8%) patients. Success rates between adults and children were comparable, despite the small number of paediatric cases (p=.19). Univariate analysis indicated that patient age, gender, weight, and location were not significantly related to intubation success.

Both studies must be interpreted with due regard for the methodological limitations associated with retrospective chart review, including the potential for incomplete, inaccurate or missing records (Bruce, 2008). Nonetheless, the apparent decline in advanced airway management success rates in the Ottawa system is acknowledged as an area of concern (Tam et al., 2009). Reliable verification of successful prehospital endotracheal intubation is a particular challenge in prehospital airway management studies, especially those employing retrospective case review where reporting bias may represent a significant confounder (Wang & Yealy, 2006b). Rocca et al. provide limited details regarding the methods used to verify endotracheal tube placement in their preliminary study, and acknowledge that the lack of emergency physician verification of tube placement is a major limiting factor. It was reported that future prehospital documentation in this system would require physician signature to verify proper endotracheal tube placement, and that oesophageal syringe detectors had been introduced to improve detection of oesophageal intubations, implying that these may not have been available during the initial study period. Consideration was also to be given to limiting nasotracheal intubation, although the frequency with which Ottawa paramedics perform this procedure has remained largely unchanged (Tam et al., 2009).

Results from the 2009 study provide far more detail of procedures employed by paramedics to confirm endotracheal tube position, which include the use of capnometry in addition to an oesophageal syringe detector, although physician verification of endotracheal intubation is not discussed (Tam et al., 2009). It is therefore possible that multiple and more reliable methods of confirmation of endotracheal intubation simply unearthed a previously unidentified level of unrecognised oesophageal intubation (Silvestri et al., 2005). Another explanation acknowledged by the authors is the reduction in opportunities for both hospital based training in advanced airway management and a dilution of procedural exposure associated with the rise in the number of paramedics within this system capable of performing advanced airway management. Although the number of paramedics more than tripled in the intervening period, demand for advanced airway procedures remained relatively constant (Tam et al., 2009). A recent meta-analysis of prehospital airway management across a range of EMS services also reported a historical decline in endotracheal intubation success rates, suggesting potential causative factors similar to those identified by Tam and colleagues (Hubble, Brown, et al., 2010).

Other retrospective studies have investigated prehospital airway management success rates in a variety of USA systems, ranging from those that only permit endotracheal intubation without pharmacological adjuncts (Garza, Algren, Gratton, & Ma, 2005) to those also utilising either sedation only (Wang, O'Connor, Schnyder, Barnes, & Megargel, 2001) or sedation and neuromuscular blockade (Bulger et al., 2002) when required. Garza et al. retrieved records from an urban Midwestern ambulance service quality improvement database for paediatric and adult cardiac arrests attended between January 1997 and July 2002. Verification of endotracheal tube position was performed by the receiving emergency physician and recorded on a quality assurance form. An endotracheal intubation attempt was defined as insertion of the laryngoscope past the teeth in an attempt to view the glottis, whereas failure was defined as inability to insert an endotracheal tube into the trachea as defined by the emergency physician. The overall aim of this study was to analyse factors associated with intubation non-attempt or failure between different patient populations.

A total of 2,669 oral endotracheal intubations were recorded during the study period. Intubation was attempted in 71% (n=86) of paediatric cases, 67% (n=182) of adult traumatic arrest cases and 96% (n=2401) of adult medical arrest cases. Failure rates for each cohort were 44.2%, 29.7% and 14.7% respectively. Variation in endotracheal intubation attempt rates suggests that paramedics in this system may exhibit selection bias relating to decisions regarding prehospital advanced airway management. Some evidence exists that prehospital clinicians perceive endotracheal intubation in trauma to be more challenging (Thomas, Abo, & Wang, 2007) and that children are less likely than

adults to receive advanced life support interventions by paramedics (Kumar, Bachman, & Kiskaddon, 1997). Lack of pharmacological adjuncts to facilitate endotracheal intubation in non-arrest patients may also explain lower attempt rates and higher failure rates in the trauma group (Davis, Ochs, et al., 2003).

When compared with the adult medical arrest group, a significantly increased relative risk (RR) of intubation failure was noted for the paediatric (RR 3.01, 95% CI 2.33-3.88, p<.001) and adult traumatic arrest (RR 2.02, 95% CI 1.58-2.57, p<.001) cohorts. These trends are consistent with those observed by Tam and colleagues, where Ottawa paramedics achieved the highest endotracheal intubation success rates in cardiac arrest patients and the lowest in paediatric cases (Tam et al., 2009). The use of nasotracheal intubation, which was not available to the paramedics investigated by Garza et al. and appears universally associated with relatively lower success rates (Hubble, Brown, et al., 2010), may limit the extent to which comparisons can be made. However, previous research conducted within the Ottawa system suggests these trends persist when nasotracheal intubations are excluded from analysis. The requirement for physician verification of endotracheal tube position potentially strengthens the validity of these findings (Jones, Murphy, Dickson, Somerville, & Brizendine, 2004), although the number of cases where this was documented as per protocol and the incidence of unrecognised oesophageal intubation are not reported.

Two further retrospective studies employed chart review to quantify airway management success rates in systems where a proportion of endotracheal intubations are pharmacologically assisted (Wang et al., 2001; Bulger et al., 2002). Wang et al. examined data relating to all endotracheal intubation attempts from January to December 1998 (n=893) in Delaware State, where paramedics respond to all calls and are authorised to perform nasal and oral endotracheal intubation and sedation facilitated intubation using midazolam as required. Bulger et al. retrieved comparable data from the Seattle Fire Department for the period January 1997 to November 1999 (n=2,700). Of note, paramedics in the Seattle system are selectively targeted to calls as part of a tiered response, utilise sedation and neuromuscular blockade to facilitate intubation, perform retrograde intubation and surgical airways, and are discouraged from attempting nasotracheal intubation.

Delaware paramedics attempted endotracheal intubation in 3.4% (n=893) of patients attended during the study period, achieving an overall success rate of 86.6% (n=771). The overall success rate for the 5.4% (n=2,614) of patients with an endotracheal intubation attempt by Seattle paramedics was 98.4%. Elapsed time to intubation for successful cases or time to hospital arrival for failed attempts were available for 87.3% (n=780) of patients attended in Delaware. The mean and median times to endotracheal intubation for successful cases were 8.8 minutes (95% CI 8.2-9.4) and 6

minutes (95% CI 6-6) respectively. Corresponding times for hospital arrival in failed endotracheal intubation cases were 26.1 minutes (95% CI 24.4-27.8) and 25 minutes (95% CI 23-27).

A significant difference in endotracheal intubation success rates between Delaware cardiac arrest (93.2%) and non-cardiac arrest (72.9%) patients was observed (OR 5.13, 95% CI 3.41-7.73, p<.001). Non-cardiac arrest patients (n=302), including those sedated with midazolam (n=88), were significantly more likely to be successfully intubated using an oral (78.5%) versus nasal (59.1%) approach (OR 2.53, 95% CI 1.48-3.42, p<.001). There was no significant difference in success rates between non-cardiac arrest patients undergoing midazolam facilitated intubation versus non-pharmacologically assisted intubation (OR 1.09, 95% CI 0.63-1.09, p=.75). In Seattle, cardiac arrests accounted for a lower percentage of total patients undergoing advanced airway management than in Delaware (36% versus 66.2%). In contrast with the lower rates of sedation facilitated intubation and subsequent endotracheal intubation success rates (71.6%) reported by Wang et al., Seattle paramedics employed drug facilitated intubation incorporating paralytics in 48.4% of cases (n=1,264), achieving a success rate of 97.8%.

Important methodological and system based factors may account for the variation in success rates between Delaware (Wang et al., 2001) and Seattle (Bulger et al., 2002). Wang et al. retrieved data for a year, whereas Bulger et al. incorporated almost 3 years of data in their analysis. Although cardiac arrest intubation success rates in both studies compare favourably with results from an initial retrospective study of intubations in Ottawa during 1997 (Rocca et al., 2000), a significant decline in success rates over time was subsequently noted in this system (Tam et al., 2009). Differences in airway management procedures available to paramedics in each system are likely to have influenced results. Evidence suggests that endotracheal intubation success rates improve significantly when paralytics are available to paramedics in cases where airway reflexes remain intact (Davis, Ochs, et al., 2003). Conversely, discouraging the use of nasotracheal intubation in favour of orotracheal and drug assisted approaches is also likely to have improved results in Seattle (Hubble, Brown, et al., 2010). Variations in the dispatch models employed in each study may also be important, given that increased exposure to advanced airway management opportunities has been linked to procedural success (Warner et al., 2010).

3.2.1 Summary

Overall, retrospective studies tend to be older and subject to the methodological limitations associated with retrospective methodology including missing data and issues inherent in the analysis of data not primarily collected for research purposes (Riffenburgh, 2006). Sample sizes are often small and some studies report procedural success rates for techniques that have largely become

obsolete, such as nasotracheal intubation. Considerable heterogeneity is present in terms of both study populations and clinical scope of practice, with some studies incorporating paediatric and trauma patients and others reporting results from pharmacologically assisted airway management in some cases. Appreciable variation in procedural success rates is apparent, which may in part be related to system factors, practitioner scope of practice, aetiology and practitioner education and exposure. Methods for confirmation of endotracheal intubation and definitions and means of verification of adverse events also vary considerably.

3.3 Paramedic intubation success rates – prospective studies

In contrast to the retrospective approaches adopted in the studies above, more recent research has focussed on prospective observational approaches to determine airway management success rates. Although retrospective studies are less time consuming and costly due to reliance on pre-existing established data sets, prospective approaches provide the opportunity for more comprehensive outcome data, control for confounding, and examination of causation (Woodward, 2014). The prospective studies reviewed below therefore offer an opportunity to develop a more comprehensive understanding of factors affecting procedural success rates in out-of-hospital cardiac arrest.

Two USA studies assessed prehospital endotracheal intubation attempts in Denver, Colorado using a combination of prospective and retrospective data (Colwell et al., 2005; Denver Metro Airway Study Group, 2009). Colwell et al. enrolled patients undergoing endotracheal intubation by paramedics in a single EMS system between March 2001 and May 2001, whereas the Denver Metro Airway Study Group investigators recruited patients during September 2004 to January 2005 from a wider geographical area served by 34 emergency medical, aeromedical and fire department services employing a combination of emergency medical technicians, paramedics and flight nurses. Intubation attempts were variously defined as a single pass of an endotracheal tube into the oral or nasal cavity (Colwell et al., 2005) and insertion of a laryngoscope with the intent to intubate or an attempt to pass an endotracheal tube into the trachea (Denver Metro Airway Study Group, 2009).

Either continuous waveform or colorimetric $ETCO_2$ was required to confirm endotracheal tube placement, coupled with at least one additional technique in the earlier study (direct visualisation of the tube passing through the cords, auscultation of lung sounds, absence of sounds over the epigastrium, normal oxygen saturation or observed clinical improvement) and at least two additional techniques in the more recent study (direct visualisation, noting the depth of the tube at gum/teeth line, or listening to the lungs bilaterally and over the epigastrium). In both studies, clinicians prospectively enrolled patients by completing a study specific questionnaire relating to the type of

intubation technique, number of attempts, methods of confirmation and failed airway management. Colwell et al. retrospectively reviewed hospital and autopsy records to confirm endotracheal tube placement, whilst the Denver Metro Airway Study Group collected this data prospectively where receiving emergency department physicians confirmed placement and retrospectively via the coroner where patients died in the field and were not transported. Colwell et al. regarded any removal of a prehospital endotracheal tube by the emergency physician as an unrecognised oesophageal intubation, unless an alternative reason for removal was documented. In cases where prospective data confirming endotracheal tube placement were missing, Denver Metro Airway Group investigators reviewed hospital notes to determine endotracheal tube position retrospectively on the basis of expert judgement.

Colwell et al. identified 300 patients who had undergone an intubation attempt during the study period, and were able to obtain complete data for 278 (93%) of these. Corresponding values for the Denver Metro Airway Study Group were 926 patients with complete data available for 825 (97.5%), although endotracheal tube position was determined prospectively in 636 (68.7%) and retrospectively in 290 (31.3%) of these patients. The proportions of patients declared dead in the field were similar between the two studies (9% versus 9.7%). Colwell et al. reported the number of unavailable records as proportionate across all receiving hospitals and the coroner, whereas the Denver Metro Airway Study Group were only able to retrieve data in 33.8% (n=27) of cases referred to the coroner.

Overall combined nasal and oral endotracheal intubation success rates in each study were 84.2% (Colwell et al., 2005) and 74.8% (Denver Metro Airway Study Group, 2009) respectively. Only Colwell et al. report success rates stratified according to oral versus nasal techniques. Successful placement was achieved in 97% (n=120) of patients undergoing oral intubation and in 74% (n=114) of patients undergoing nasal intubation, although 30% (n=14) of these subsequently had oral intubation attempted with a success rate of 64% (n=9). Unrecognised oesophageal intubation was identified in 0.7% of patients by Colwell et al. and in 2.4% by the Denver Metro Airway Study Group. Colwell et al. identified that one further nasotracheal tube had been malpositioned in the oropharynx and that epistaxis had occurred in 12% of patients in whom nasotracheal intubation was attempted (n=18). No further complications were identified in patients undergoing orotracheal intubation. Additional complications identified by the Denver Metro Airway Study Group included malpositioning of the tube in the oropharynx (n=11) and other sites (n=7). These complications occurred more frequently in patients intubated nasally versus those intubated orally (8.6% versus 3.4%). Patients in whom intubation attempts failed were managed using basic life support measures

in both studies. Alternative approaches were used in 5 patients in the Denver Metro Airway Group study, and included use of the combitube (n=2), laryngeal mask airway (n=2) and one cricothyrotomy that was subsequently found to be malpositioned.

The Denver Metro Airway Study Group further investigated predictors of tube malposition on arrival in the emergency department, although the majority of these failed to reach statistical significance. Patients in cardiac arrest were more likely to be successfully intubated than non-arrest patients (81.9% versus 67.6%). Only 77.3% of patients had $ETCO_2$ use documented, with colorimetric devices used in 92.8% (n=470) and waveform capnography in 7.1% (n=36) of these cases. Correct tube placement was more likely to occur when $ETCO_2$ monitoring was used (OR 1.54, 95% CI 0.68-3.29) and where ≥3 methods were used to confirm tube position (OR 2.28, 95% CI 0.99-5.04), although these results should be interpreted with caution given the wide confidence intervals. When compared with paediatric patients, non-paediatric cases were more likely to be successfully intubated (OR 6.9, 95% CI 1.42-26.2). Successful intubation was less likely in trauma versus medical patients (OR 0.59, 95% CI 0.17-1.59).

In keeping with results reported from retrospective studies in Ottawa (Rocca et al., 2000; Tam et al., 2009), the Denver studies appear to demonstrate a decline in intubation success rates and an increase in complication rates over time, coupled with lower intubation success rates in paediatric and trauma patients. The apparent inferiority of and complications associated with nasotracheal intubation are again highlighted. However, it should be noted that the same geographical areas and service were compared in the Ottawa studies, whereas the more recent Denver study (Denver Metro Airway Study Group, 2009) recruited patients from a wider geographical area and range of services than the earlier study (Colwell et al., 2005). It may therefore be that the apparent decline of overall intubation success rates is representative of relatively poorer performance in some of the other services studied, rather than a genuine decline in procedural performance by all paramedics. The different definitions of an intubation attempt used in each study may also provide a potential explanation for the observed variation in success rates. The definition developed by Colwell et al. incorporated passage of an endotracheal tube into the oral or nasal cavity, whereas the Denver Metro Airway Study Group regarded instrumentation of the airway with a laryngoscope as an attempt to intubate orally. The Denver Metro Airway Group Study is therefore based on an intention-to-treat approach, which captures cases where paramedics intended to intubate the patient but subsequently elected not to attempt to pass an endotracheal tube. In contrast, Colwell et al. would not have captured data on cases where paramedics instrumented the airway but then elected not to proceed any further with the intubation attempt, potentially excluding patients where

paramedics encountered problems or determined that they would experience procedural difficulties. This has the potential to have introduced an appreciable element of selection bias which is not present to the same extent where an intention-to-treat approach is taken (Peat, 2002).

A further prospective USA study sought to stratify intubation success rates according to the number of attempts required to accomplish the procedure (Wang & Yealy, 2006a). The study recruited patients in whom intubation was attempted during January 2003 to June 2004 by paramedics, nurses and physicians drawn from 42 emergency medical service providers in the Pennsylvania region. Most services had the capability to perform sedation facilitated intubation, with rapid sequence intubation incorporating paralytics limited to air medical providers. Clinicians completed a study specific questionnaire after each intubation attempt, providing details relating to the patient, clinical circumstances, course of airway management, adverse events, complications and initial outcome. An orotracheal intubation attempt was defined as any insertion of a laryngoscope blade into the mouth. The corresponding definition for nasotracheal intubation was any insertion of an endotracheal tube through the nares. Correct positioning of the endotracheal tube was confirmed solely via prehospital records and did not include verification by receiving Emergency Department clinicians.

The primary outcome measure was rescuer reported success stratified according to the number of attempts required to achieve endotracheal intubation. Overall success was calculated according to the outcome on the last recorded intubation attempt, with no further analysis performed in cases where more than six attempts were made. Through the use of univariate odds ratios and exact 95% confidence intervals, investigators identified the number of attempts in which the cumulative success rate approached the overall success rate by establishing the earliest intubation attempt where the odds ratio between cumulative and overall success was statistically non-significant. Cardiac arrests, non-drug assisted intubations of patients with perfusing rhythms, sedation facilitated intubations, and rapid sequence intubations were analysed separately to account for the potential effects of different clinical characteristics on airway management success rates.

Of 1,953 intubation attempts, procedural success data were available for 99.4% (n=1,941) of cases. Cardiac arrests accounted for the majority of airway procedures (n=1,272), followed by non-drug assisted intubation (n=463), sedation facilitated intubation (n=126) and rapid sequence intubation (n=80). Paramedics performed the intubation in 94% of these cases. Total success rate across all groups was 87.1%, with over 30% of patients undergoing more than one intubation attempt. There were no cases in which more than 6 attempts were performed. Overall success rate for cardiac arrest patients was 91.8% (95% CI 90.2%-93.3%), with cumulative success progressing from 69.9% to

84.9% and 89.9% on the second and third attempts respectively. Cumulative success approached overall success by the third attempt in this subgroup (OR 0.79; 95% CI 0.61-1.04). Overall success rate for non-drug assisted intubation of patients with a perfusing rhythm was 73.7% (95% CI 63.4%-77.6%). First, second and third attempt cumulative success rates were 57.6%, 69.2% and 72.7% respectively, with second attempt cumulative success approaching overall success (OR 0.80, 95% CI 0.6-1.07). For patients undergoing either sedation facilitated or rapid sequence intubation, overall success rates were 77.0% (95% CI 68.6%-84.0%) and 96.3% (95% CI 89.4%-99.2%) respectively. Corresponding cumulative success rates were 44.4% and 56.3% on first attempt, 62.7% and 81.3% on second attempt and 75.4% and 91.3% on third attempt. In both sub-groups, third attempt success approached overall success rates (OR 0.92 95% CI 0.51-1.64 and OR 0.41, 95% CI 0.10-1.65). These techniques were only available to selected ground paramedics and aeromedical crews (Wang & Yealy, 2006a), and are therefore not representative of general trends in procedural success rates within the wider EMS system in this study.

Older studies involving smaller cohorts have identified similar trends, with Stewart et al. observing cumulative success rates of 57.9%, 84.0% and 89.5% in a series of 779 cardiac arrest or deeply comatose patients (Stewart, Paris, Winter, Pelton, & Cannon, 1984), and Pointer et al. reporting corresponding success rates of 64.8%, 87.5% and 92.7% in a sample of 383 patients (Pointer, 1989). Lower success rates were seen in non-arrest and trauma cases. The more recent retrospective study performed by Rocca et al. discussed above reported marginally higher cumulative success rates of 80.1%, 90.7% and 95.2%, again with lower rates for non-arrest and trauma patients (Rocca et al., 2000). The apparent decline in success rates for non-arrest and trauma patients observed in many studies is perhaps unsurprising, given that many of these patients were managed using techniques such as nasotracheal intubation and sedation facilitated intubation, which a recent meta-analysis confirms are inferior to the more sophisticated but potentially more complex and risk laden procedure of rapid sequence intubation (Hubble, Brown, et al., 2010). Indeed in the larger prospective series of 1,941 patients considered here, only 80 underwent rapid sequence intubation by air medical crews. These providers conventionally have more experience in performing airway management, and this, coupled with the apparent superiority of rapid sequence intubation, may account for the appreciably higher cumulative success rates in this sub-group (Davis et al., 2005).

3.3.1 Summary

As discussed previously, considerable heterogeneity in practitioner training, system design, procedural protocols and clinical characteristics of patients renders meaningful comparisons between studies problematic. Although Wang and Yealy report results from 42 independent

advanced life support agencies, the study design did not quantify individual intubation success rates for each service. It is therefore difficult to ascertain whether the relatively low overall success rates for endotracheal intubation reported are the result of universally poor procedural performance amongst all practitioners or are the product of certain providers or services achieving unusually low success rates, thus skewing data and adversely affecting total success rate. Nonetheless, a common trend in all studies investigating cumulative success rates in prehospital airway management is that any further improvement in success rates after three attempts is likely to be, at best, negligible. For this reason, the authors recommend that prehospital intubation attempts should be limited to a maximum of three attempts.

3.4 Influence of geographical and environmental factors on intubation success rates

The out-of-hospital environment in which EMS providers operate is very different to the hospital setting and poses unique challenges both in terms of clinical practice and research (Lyon, Egan, Gowens, Andrews, & Clegg, 2010). Factors such as weather, behaviour of bystanders, availability of resources and equipment, environmental constraints and safety issues may affect the performance of prehospital clinicians to a greater extent than hospital practitioners (Garza, Gratton, McElroy, Lindholm, & Coontz, 2008). In view of this, understanding the impact of these factors on actual and perceived performance of key airway management tasks is important in assessing the extent to which this may affect procedural success rates.

Various researchers have investigated the influence of geographical location and environmental factors on airway management success rates. In a retrospective chart review, McIntosh et al. sought to quantify rapid sequence intubation success rates amongst Utah flight nurses and paramedics, stratified according to the location of the intubation attempt, patient characteristics and aircraft type (McIntosh, Swanson, McKeone, & Barton, 2008). Garza et al. conducted a prospective, observational descriptive study of environmental factors encountered during endotracheal intubation of adult medical cardiac arrest patients by paramedics in an advanced life support service in Midwest USA (Garza et al., 2008). The purpose of this study was to ascertain the incidence of adverse factors rather than to quantify intubation success rates according to the number and type of these factors encountered during individual intubation attempts.

Retrospective chart review by McIntosh et al. between January 1995 and May 2007 identified 939 patients requiring intubation by air medical crews, with complete data available for 936 cases (McIntosh et al., 2008). Overall intubation success rate, defined as placing a cuffed tube in the trachea via non-surgical means, was 96%. The cricothyroidotomy rate was 1.9%, with all other patients managed using the Laryngeal Mask Airway or via bag-valve-mask ventilation. Success rates

by location are shown below (Table 1). There was a significantly lower success rate for intubation in transit versus scene or hospital intubations (p=.002). Age, gender, clinical characteristics and type of aircraft did not significantly influence intubation success.

Table 1 Intubation success rates by location (McIntosh et al 2008)

Location	**Number successful**	**% of overall total**	**% success**
Scene	595/627	67	94.9
En-route	60/67	7.2	89.6
In-flight	57/64	6.1	89
Ambulance	3/3	0.3	100
Referring hospital	232/235	25.1	98.7
Receiving hospital	7/7	0.7	100

In preparation for a related prospective study, Garza and colleagues assembled a group of emergency medical service clinicians with extensive field experience to identify and reach consensus on environmental factors felt to be important in affecting the ease with which intubation may be performed in the prehospital setting (Garza et al., 2008). Six constructs were identified, namely scene distractions, adequate lighting, physical space during the intubation attempt, location where intubation was attempted, paramedic intubating position, and patient position. Multiple specific items were developed for each construct and a study-specific data collection tool developed to enable participating paramedics to indicate individual factors encountered during each intubation attempt, regardless of whether the patient was successfully intubated.

Data were collected from September 2000 to September 2004. Unlike the air medical crews discussed above, paramedics in this system do not utilise any form of drug assisted intubation. A total of 1,396 medical cardiac arrest patients met the inclusion criteria for the study, with completed forms available for 1,235 of these, yielding a completion rate of 88.5%. 1,658 intubation attempts were performed on these patients, with an overall success rate of 85% (95% CI 83%-97%). Frequency analysis of the environmental constructs revealed that paramedics most frequently attempted intubation inside buildings (n=1,239, 75%) kneeling at the head (n=899, 54%) of a supine patient (n=1,653, 93%) usually with adequate lighting (n=1,271, 77%) but often with sub-optimal space (n=655, 40%). Significant scene distractions, such as bystanders or safety concerns, were encountered in approximately 20% of cases.

3.4.1 Summary

Limited research exists specifically examining the influence of environmental factors on airway management in out-of-hospital emergency care. The evidence available suggests that environmental challenges are encountered frequently where airway management is required, and

that the location in which techniques such as endotracheal intubation are performed may significantly affect procedural success rates. Geographical and environmental factors encountered in out-of-hospital cardiac arrest present unique challenges not routinely present in other clinical settings. In some cases, the geographical location of the incident may preclude the timely provision of more skilled clinical assistance where difficulties are encountered in managing the airway. In other cases, environmental constraints such as space, patient position, weather, lighting and the behaviour of bystanders may further hinder attempts at advanced airway management including endotracheal intubation. Although evidence is limited, it is apparent that these effects may persist regardless of patient characteristics. It is important to be cognisant of these factors when analysing results from different studies given the extent to which study setting and environmental factors may affect results.

3.5 Influence of airway management approach on survival

Most of the studies discussed above have sought to quantify procedural success rates for ETI rather than assessing the influence of ETI and other airway management strategies on outcomes in out-of-hospital cardiac arrest. As the evidence base for out-of-hospital airway management in cardiac arrest has evolved, so too has the focus of research efforts from straightforward quantification of procedural success rates to more sophisticated measures of the influence of airway management on outcomes (Wang et al., 2010). This section reviews the evidence for the influence of airway management approach on outcomes in out-of-hospital cardiac arrest and is therefore of direct relevance to the primary research question.

3.5.1 Negative association between endotracheal intubation and survival – retrospective studies

Two retrospective studies conducted in US emergency medical services systems report negative associations between ETI and survival in adult cardiac arrest patients. Studnek and colleagues retrospectively obtained data relating to cardiac arrests from July 2006 to December 2008 transported to any of seven hospitals in Mecklenburg County, North Carolina via an established Ustein-style database (Studnek et al., 2010). A second study retrospectively extracted data from a combination of paramedic field records, ED records and in-hospital records for survivors of cardiac arrests transported to a Los Angeles general municipal hospital between November 1994 and June 2008 (Arslan Hanif et al., 2010). This single hospital is responsible for receiving approximately 2% of ALS and 3% of BLS transports from EMS within Los Angeles.

EMS systems in both studies employ a two-tier response system, with firefighters with BLS training used as first responders, supported by a second tier of Paramedics capable of providing ALS interventions in cardiac arrest. Paramedics in both studies are authorised to initiate ALS treatments including ETI autonomously, although further interventions once initial treatment has commenced are directed via radio or telephone by medical control physicians in the Los Angeles setting. Alternative airway devices were available to paramedics in both studies in the form of Laryngeal Mask Airways (LMA) in Mecklenburg County and Oesophageal Obturator or Combitube in Los Angeles. Pharmacologically assisted ETI is not available to paramedics in either system.

Both studies included adult patients aged >18 years with non-traumatic cardiac arrest in whom paramedics initiated resuscitative efforts, and excluded cases of drowning, electrocution, or patients where there were obvious signs of death or a valid 'do not attempt resuscitation' order was identified. Arslan Hanif et al. also excluded cardiac arrests caused by drug overdose. Studnek et al. identified 1,142 cases of cardiac arrest, with sustained ROSC reported in 299 (26.2%). Intubation was accomplished on first attempt in 557 patients (50.5%) and after multiple attempts in 132 cases (11.6%). A further 160 patients (14.0%) were not successfully intubated despite multiple attempts. ETI was not attempted in the remaining 203 patients (17.8%), although it is unclear how many of these patients were managed using an LMA or BLS measures only and why intubation was not attempted. Overall, 45.3% of patients without an ETI attempt achieved ROSC, compared with 25.3% of those with one successful ETI attempt, 17.4% of those with ROSC post multiple ETI attempts and 11.3% of those with multiple unsuccessful attempts. Univariate analysis indicated that individuals with no ETI attempt were 2.44 (95% CI 1.75-3.41) times more likely to achieve ROSC than those with one successful ETI attempt. Final logistic regression analysis controlling for presenting rhythm, witnessed arrest, gender, ethnicity and ETI attempts found similar results, with individuals in whom ETI was not attempted 2.33 (95% CI 1.63-3.33) times more likely to achieve ROSC than those with one successful ETI attempt. Of the 299 patients with prehospital ROSC, 118 (39.5%) were subsequently discharged alive from hospital. Discharge status was unknown in 48 patients (16%), and the authors classified these as not surviving to hospital discharge. Similar airway management trends were identified in the survival to discharge subset of patients, with those not undergoing ETI 4.96 (95% CI 3.22-7.67) times more likely to be discharged alive than those with one successful ETI attempt. Logistic regression analysis incorporating similar variables to those discussed earlier lends further support to a negative association between ETI and survival to discharge, with patients not undergoing ETI 5.46 (95% CI 3.36-8.90) times more likely to survive than those with one successful ETI attempt.

Corresponding values in the study by Arslan Hanif et al. were a total of 1,294 cases of non-traumatic cardiac arrest, of which 15.3% (n=197) had ROSC sustained to hospital admission, and 4.3% survived to hospital discharge. ETI was performed in 1,027 patients (79.4%), with the remaining patients managed using Bag-Valve-Mask (BVM) ventilation (10.1%), Combitube (7.9%) or Oesophageal Obutrator (2.2%). In contrast to the analysis conducted by Studnek et al., number of intubation attempts was not recorded. Five patients (0.4%) had incomplete records and it was unclear what airway management approach had been used. Comparison of BVM versus ETI revealed similar trends to those reported by Studnek et al., with patients receiving BVM 3.3 (95% CI 1.8-6.3, p=.0002) times more likely to survive to hospital discharge. Multivariate logistic regression adjusting for age, gender, presenting rhythm, witnessed arrest and bystander CPR demonstrated a similar trend, with patients managed via BVM ventilation 4.5 (95% CI 2.3-8.9) times more likely to survive to hospital discharge when compared with those undergoing ETI.

3.5.2 Positive association between endotracheal intubation and survival – retrospective studies

In contrast, several studies have identified short term survival benefits associated with paramedic ETI in specific subsets of patients in cardiac arrest. Egly and colleagues conducted a retrospective review of a cardiac arrest database maintained by a large suburban ED in Michigan to which paramedics from a combination of municipal and private provider agencies transport cardiac arrest patients according to standardised regional protocols (Egly et al., 2011). The study examined all cases of out-of-hospital cardiac arrest in patients aged >18 years that occurred between January 1995 and December 2006, with investigators manually reviewing notes to exclude cases of traumatic cardiac arrest and patients with prompt ROSC where ETI would not be indicated. During the study period, ETI was considered the preferred method of airway management in cardiac arrest, with the Combitube used as a rescue device in cases where ETI failed.

Egly et al. identified a total of 1,515 non-traumatic adult cardiac arrest cases, with 33 survivors with prompt ROSC excluded (Egly et al.., 2011). A total of 1,220 (86.2%) patients were successfully intubated, with 270 (20.2%) surviving to admission and 93 to discharge (7.0%). There was no significant difference in overall survival to discharge between the intubation and non-intubation groups (6.5% versus 10%, p=.09). In patients presenting in a shockable rhythm, the only significant predictor of survival to admission was witnessed cardiac arrest (OR 2.31, 95% CI 1.44-3.72), therefore no multivariate analysis was performed. In this patient group, ETI was negatively associated with survival to discharge (OR 0.50, 95% CI 0.26-0.93) whereas patients with a witnessed arrest were more likely to survive to discharge (OR 2.89, 95% CI 1.43-5.83). After controlling for

witnessed cardiac arrest, multivariate logistic analysis demonstrated that ETI significantly decreased survival to discharge in patients presenting in a shockable rhythm (adjusted OR 0.52, 95% CI 0.27-0.998). Conversely, in patients presenting in non-shockable rhythms ETI was a significant predictor of survival to admission (OR 2.94, 95% CI 1.16-7.44). In common with patients presenting in VF or VT, witnessed cardiac arrest remained a predictor of survival to admission (OR 2.68, 95% CI 1.46-4.91). In a multivariate logistic model for patients presenting in a non-shockable rhythm, ETI increased survival to admission (adjusted OR 2.96, 95% CI 1.04-1.83) after controlling for witnessed cardiac arrest. There were no significant predictors of survival to discharge in this patient group, therefore no further multivariate analysis was performed.

3.5.3 Positive association between endotracheal intubation and survival – prospective studies

In the context of the emerging Japanese EMS system, several studies based on review of cardiac arrest registry data have examined outcomes stratified according to airway management approach both nationally (Tanabe et al., 2013) and in single (Takei et al., 2010; Kajino et al., 2011) or multiple (Nagao et al., 2012) prefectures. Investigators in all studies reviewed data from adult patients (>15 years) without evidence of trauma who suffered out-of-hospital cardiac arrest and received CPR from Emergency Life Support Technicians (ELST) and Paramedics certified in advanced airway management, including SGA insertion and ETI. Out-of-hospital ETI has been authorised for use by selected ambulance clinicians in Japan since 2004, and the data collection periods for studies were designed to coincide with the gradual introduction of this skill. Takei et al. and Nagao et al. collected data from July 2004 to March 2008 and January 2006 to December 2007 respectively to determine firstly whether airway management via ETI would affect outcome when compared with other advanced airway devices (oesophageal obturator, oesophageal-tracheal combitube or LMA) and BVM ventilation, and secondly whether treatment by paramedics certified to perform ETI would affect outcome when compared with those not certified to perform this procedure. Primary endpoints were 1 year survival (Takei et al. 2010) and favourable neurological outcome (Nagao et al. 2012). Secondary endpoints were defined as any ROSC, sustained ROSC (palpable pulses for >20 minutes), and 1 month survival. Cerebral Performance Category (CPC) was evaluated in all patients, with good outcome defined as CPC score of 1 (good overall performance) or 2 (moderate overall disability) in patients without any neurological disturbance before the event. Patients with pre-arrest neurological impairment were regarded as having a good outcome when the pre and post resuscitation CPC categories were equivalent.

Kajino et al. and Tanabe et al. collected data from January 2005 to December 2008 and January 2005 to December 2007 for cases of witnessed out-of-hospital non-traumatic cardiac arrests and cardiac arrests of all aetiologies respectively in adults who received advanced airway management via SGA or ETI by ELST clinicians. These studies sought to compare outcomes in patients managed with ETI versus SGA insertion and, in the case of Kajino et al., investigate the influence of time to advanced airway placement on outcomes. Neither study compared advanced airway management approaches with BVM alone. Primary outcome measures were neurologically favourable survival at one month employing the CPC definition outlined above. Secondary outcome measures were ROSC, admission to hospital, and one-month survival.

Takei et al. excluded cases treated by providers who were only certified to perform BVM ventilation and patients aged less than 8 years, as paramedic ETI was not permitted in this age group. During the study period, limited numbers of paramedics were able to administer adrenaline in cardiac arrest. Both Takei et al. and Nagao et al. excluded such cases from analysis due to the potential confounding effect of drug administration on the incidence of ROSC. In contrast, both Kajino et al. and Tanabe et al. included patients administered adrenaline, but excluded all cases where no advanced airway was placed, regardless of the status of the practitioner managing the patient.

Takei et al. collated data for 2,759 out-of-hospital cardiac arrests. A total of 173 patients met study exclusion criteria, of whom 113 were treated by basic level providers not capable of performing ETI, 33 were aged <8 years, and 27 received adrenaline. Advanced airway management was attempted in 1,047 of the remaining 2,586 patients, which failed or was discontinued in 124 cases. These cases were also excluded from further analysis on the basis that the paramedics were obliged to ventilate these patients via BVM only, resulting in inadequate ventilation and a very poor long-term survival (0% at 1 month). Subsequent data analysis was therefore based on an overall sample of 2,462 patients. Of these, 263 received ETI, 660 other advanced airway management (LMA or Oesophageal Obturator), and 1,539 BVM ventilation. Nagao et al. assessed 820 cardiac arrest patients admitted to their hospital, excluding a total of 465 (56.7%) due to a range of non-cardiogenic aetiologies, those aged under 18 years and cases where adrenaline was administered (n=8). The remaining cases (n=156) were managed solely via BVM ventilation. In 199 patients ultimately escalated to advanced airway management, an ET tube was placed in 10, with the remainder ventilated via LMA (n=147) or oesophageal-tracheal combitube (n=42).

Takei et al. initially stratified data according to whether the patient had been managed by a paramedic capable of ETI or a paramedic trained only in alternative airway management devices. Median time to transfer patients to the ambulance was significantly longer when an intubation

trained paramedic attended the patient (12 minutes versus 11 minutes, p<.0001), although this is unlikely to be clinically significant. When compared with paramedics not trained in intubation, patients attended by intubation-trained paramedics were significantly more likely to achieve any ROSC (p=.0308) and sustained ROSC (p=.0012). However, there were no statistically significant differences when the same analysis was applied to the cardiac and non-cardiac aetiology sub-groups, although a non-significant trend towards increased incidence of sustained ROSC was noted where non-cardiac patients were managed by an ETI trained practitioner (p=.0515). Univariate analysis employing Tukey's method demonstrated that the incidence of any form of ROSC was significantly higher in patients undergoing ETI (n=81, 31.6%) when compared with other advanced airway devices (n=152, 23%) and BVM ventilation (n=366, 23.8%, p=.0158). Corresponding values for sustained ROSC were 30% ETI (n=79), 20.2% other advanced devices (n=133) and 21.3% BVM (n=327, p=.0028). In patients with arrests of non-cardiac origin, rates of ROSC differed significantly between the three groups, with patients undergoing ETI more likely to achieve any ROSC (p=.0321) and sustained ROSC (p=.0090) (Table 2).

Table 2 Comparison of outcomes among airway management groups in patients with out-of-hospital cardiac arrest of non-cardiac origin (Takei et al 2010)

Outcomes	**ETI**	**Other AAM**	**BVM**	***P* value**
Any ROSC	51 (39%)	72 (24.4%)	197 (26.4%)	.0321
Sustained ROSC (pulse >20 mins)	50 (35.2%)	66 (22.4%)	179 (24.0%)	.0090
Sustained ROSC with favourable neurological condition	1 (0.9%)	3 (1.0%)	11 (1.5%)	.6863
Alive or discharged alive at 1 month	8 (5.6%)	5 (1.7%)	33 (4.4%)	.0633
Alive or discharged alive at 1 year	4 (2.8%)	4 (1.4%)	21 (2.8%)	.3742

A direct comparison of ETI versus other advanced airway devices that excluded data relating to BVM ventilation demonstrated a significant increase associated with ETI in relation to survival rates at one month. Clinical outcomes did not differ significantly when the same analyses were applied to arrests with a presumed cardiac aetiology. Similar trends were identified by Nagao and colleagues (Nagao et al., 2012), who exclusively examined arrests of presumed cardiogenic aetiology and found significantly higher rates of any ROSC amongst patients undergoing advanced airway management versus BVM ventilation alone (18.6% versus 10.3%, p=.0352) and higher rates of intensive care admissions (12.6 versus 4.5%, p=.0089). This relationship persisted following multivariate regression analysis incorporating age, bystander CPR, initial ECG rhythm and interval from emergency call to ED arrival, which demonstrated increased odds of any ROSC associated with advanced airway management (OR 1.960, 95% CI 1.015-3.785). There was no significant variation in the incidence of

survival with good neurological outcome between the various airway management groups (p=.2168).

Kajino et al. reviewed a total of 26,303 cases of cardiac arrest. Resuscitation was attempted in 26,303 patients, of whom 1,352 had suffered traumatic cardiac arrest and were excluded from further analysis. Of the remaining 22,470 cases of non-traumatic cardiac arrest, 7,517 were witnessed by bystanders and formed the basis for subsequent data analysis. Of these, 5,377 received advanced airway management, consisting of ETI in 1,679 patients and LMA insertion in 3,698. No advanced airway management was performed in 2,055 patients and in 85 cases the approach was unknown. Tanabe et al. identified a total of 308,710 patients where resuscitation was attempted. Cases where no advanced airway management was performed (n= 167,953) or the type of airway device employed was unclear (n=2,169) or unknown (n=340) were excluded. Of the remaining cases, 12% underwent ETI (n=12%, n=16,054), with the remainder managed via LMA (25%, n=34,125) or oesophageal obturator (63%, n=88,069).

Kajino and colleagues found that in comparison with SGA insertion, ETI was associated with increased collapse to airway placement time (17.2 minutes versus 15.8 minutes, p<.001) and collapse to hospital arrival time (33.9 minutes versus 30.3 minutes p<.001). In contrast to the findings of Takei et al., Kajino et al. reported that, after adjusting for confounding variables, the presence of an ETI-trained ELST was associated with an increase in favourable neurological outcome (adjusted OR 1.86, 95% CI 1.04-3.34, p<.01). Time to placement of any advanced airway was also a significant predictor of survival (adjusted OR 0.91, 95% CI 0.88-0.95, p<.001). Subsequent analysis of odds of favourable neurological outcome by quartile time to advanced airway management demonstrated that the percentage of patients with CPC scores ≤ 2 declined as time to advanced airway placement increased. This relationship persisted regardless of the presenting ECG rhythm. Comparison of patients managed via ETI versus SGA demonstrated that ETI was associated with a higher incidence of ROSC (16.6% versus 10.1%, p<.001) and ROSC sustained to the emergency department (47.8% versus 44.4%, p=.002). A significantly higher proportion of patients managed via ETI were administered prehospital adrenaline (27.1% versus 5.9%, p<.001). Similarly, Tanabe et al. found that rates of ROSC before hospital arrival in the LMA (4.9%) and oesophageal obturator (4.41%) groups were significantly lower than those in the ETI group (7.24%, p<.001) for cardiac arrests of all aetiologies. One month survival rates were also lower in the LMA (3.64%) and oesophageal obturator groups (3.85%) than the ETI group (4.19%, p=.003). These relationships persisted when multivariate logistic regression analysis was undertaken. Tanabe and colleagues conducted further subgroup analyses, stratifying arrests as either endogenous (cardiac, respiratory

or cerebrovascular origin and tumours) and exogenous (trauma, drowning, asphyxia, overdose and hanging), with arrests of endogenous origins accounting for 84% of cases. In this analysis, after adjustments for confounders, rates of favourable neurological outcome for survivors at one month were marginally but significantly lower in the LMA (1.05%) and oesophageal obturator (1.15%) groups than the ETI group (1.25%, p=.025). In contrast, Kajino et al. found comparable rates of neurologically favourable survival at one month between the ETI and SGA groups 3.6% versus 3.6%, p=.945) for cases of witnessed non-traumatic cardiac arrest.

3.5.4 Negative association between any form of advanced airway management and survival compared with bag-valve-mask ventilation alone – propensity scored matched database analyses

Two similar studies employing propensity score matched analysis were undertaken in Korea by Shin and colleagues and in Japan by Hasewaga et al. (Shin, Ahn, Song, Park, & Lee, 2012; Hasegawa, Hiraide, Chang, & Brown, 2013) consisting of retrospective reviews of national databases to determine the association between airway management approach and survival of out-of-hospital cardiac arrest patients. Propensity matching selects cases and controls with similar combinations of confounders (Woodward, 2014). Patients were classified as receiving ETI, LMA insertion or BVM ventilation only. Survival to hospital admission and survival to hospital discharge formed primary and secondary outcome measures respectively in the analysis conducted by Shin et al., whereas Hasewaga et al. defined the primary study endpoint as favourable neurological outcome (CPC 1&2) at one month post arrest, with secondary outcomes identified as ROSC before hospital arrival and one month survival. Shin et al. reviewed ambulance electronic records to identify out-of-hospital cardiac arrests from January 2006 until December 2007 prior to attending the receiving hospital to review clinical notes and abstract data using an Utstein style template. Data were collected for patients of any age who suffered cardiac arrest of presumed cardiac aetiology. Patients who did not receive CPR in the field or on arrival at hospital were excluded. Hasegawa et al. reviewed records from the All-Japan Utstein Registry of the Fire and Disaster Management Agency to identify adult (>18 years) cases of cardiac arrest occurring between January 2005 and December 2010. Neither ELST clinicians in Japan nor Emergency Medical Technicians (EMTs) within Korean ambulance services are permitted to terminate resuscitation, therefore all patients in whom CPR was attempted would have been transported to hospital in both studies. Two levels of EMT exist within the Korean ambulance system, with only level 1 EMT staff permitted to perform ETI or LMA insertion. Any patients not attended by EMT 1 staff during their prehospital resuscitation attempt were therefore

also excluded from the analysis. This contrasts with the Japanese system, where an ambulance crew usually consists of one ELST clinician capable of performing advanced airway management incorporating SGA and in some cases ETI.

Shin et al. identified a total of 54,496 cases of cardiac arrest, although outcomes were unknown for 2,096 (3.7%) of these which were excluded from further analysis. Other exclusions included patients with arrests of non-cardiac aetiology (n=20,536, 37.7%), cases not treated by EMS providers (n=8,250, 15.6%), cases not treated by ED physicians (n=11,121, 20.4%), and cases treated exclusively by level 2 EMTs (n=7,012, 12.9%). Of the remaining 5,278 patients attended by level 1 EMTs, 4,637 (87.9%) were ventilated via BVM, 391 (7.6%) via LMA insertion, and 250 (4.7%) via ETI. Unadjusted survival-to-admission rates were 22% in the ETI group, 20.5% in the LMA group and 20.1% in the BVM group. Corresponding values for survival to discharge were 8% in the ETI group, 5.6% in the LMA group and 7.0% in the BVM group. Comparison of ETI versus BVM via propensity score matched analysis demonstrated no significant difference in survival to admission or survival to discharge between the two airway management groups. The same analysis applied to the LMA group versus the BVM group demonstrated no difference in survival to admission but revealed a significantly lower rate of survival to discharge in the LMA group (5.7% versus 9.6%, p=.04). In a multivariate regression analysis of data not subject to propensity score matching, survival to discharge and survival to admission were similar for ETI versus BVM (OR 0.91, 95% CI 0.66-1.27 and OR 1.00, 95% CI 0.60-1.66). Both survival to admission and to discharge were significantly lower for patients managed via LMA when compared with BVM (OR 0.72, 95% CI 0.54-0.95 and OR 0.52, 95% CI 0.32-0.85). Multivariate regression analysis applied to propensity matched samples again demonstrated no significant differences in adjusted survival to admission and to discharge between the ETI and BVM groups (OR 1.32, 95% CI 0.81-2.16 and OR 1.44, 95% CI 0.66-3.15). In this analysis, no significant difference in survival to admission between the LMA and BVM groups was found (OR 0.72, 95% CI 0.50-1.02), however survival to discharge was again found to be significantly lower in the LMA group versus the BVM group (OR 0.45, 95% CI 0.25-0.82).

Hasegawa et al. identified a total of 658,829 adult patients with out-of-hospital cardiac arrest, and excluded 295 patients where the airway management approach was unknown. Of the remaining 649,359 patients, 56.7% (n=376,837) were managed with BVM alone, with the remaining 281,522 patients undergoing advanced airway management via ETI (6.5% n=41,972) or SGA (36.9%, n= 239,550). Rates of neurologically favourable survival were 1% in the ETI group, 1.1% in the SGA group and 2.9% in the BVM group (p<.01). Unadjusted analysis for all other secondary end points demonstrated similar significant negative associations between any form of advanced airway

management and outcomes (p<.01). Adjusted odds of favourable neurological outcome were 0.51 (95% CI 0.45-0.56) for ETI and 0.52 (95% CI 0.49-0.54) for SGA demonstrating the persistent nature of the relationship between poor neurological outcome and any form of advanced airway management. Analysis incorporating propensity-matched patients demonstrated similar results, with adjusted odds ratios of 0.45 (95% CI 0.37-0.55, p<.001) for ETI and 0.36 (95% CI 0.33-0.39, p<.001) for SGA when compared with BVM alone.

Overall, neither Takei et al. nor Kajino et al. were able to demonstrate any association between ETI or indeed any other specific airway management approach and long term survival or favourable neurological outcome. In addition, Hasweaga et al. comment that the previous analysis of Japanese data undertaken by Nagao et al. reporting a significant relationship with advanced airway management and ROSC but not favourable neurological outcome was probably underpowered. However, these results must be interpreted in the context of evolving EMS systems within Japan and Korea, which are characterised by a high degree of medical control and relative inexperience with out-of-hospital advanced airway management than other systems in areas such as the UK, North America, South Africa and Australasia (Trevithick, Flabouris, Tall, & Webber, 2003; Pozner, Zane, Nelson, & Levine, 2004; MacFarlane, van Loggerenberg, & Kloeck, 2005). Whereas paramedics in these systems have sufficient autonomy to determine the airway management strategy on a case-by-case basis, providers in the Japanese and Korean systems require on-line medical consultation and permission to proceed before undertaking certain forms of advanced airway management. There is therefore significant selectivity in the use of such devices by proxy, often in cases where existing airway management approaches have proven inadequate. The use of advanced airway manoeuvres in such studies may therefore be a marker for more complex clinical cases with potentially worsened outcomes. Where advanced airway management is approved in this context, certain devices such as the oesophageal tracheal combitube and the oesophageal obturator airway have been associated with poor prehospital procedural success rates (Hubble, Wilfong, Brown, Hertelendy, & Benner, 2010) and have either been withdrawn from practice or are not in widespread use in other more established systems. This may be of particular significance in studies where a range of extraglottic devices are considered as a homogenous group for the purposes of comparison with ETI and/or BVM. The inability of Japanese and Korean providers to terminate resuscitation in the field or to recognise death in all but the most unequivocal of cases and the resultant need to transport large volumes of patients to the ED with resuscitation ongoing renders meaningful comparison between these cohorts of patients and results from other studies problematic where paramedics are permitted to recognise death or terminate resuscitative efforts according to established criteria. In addition, as a result of airway management procedures and on-

line medical control, the proportion of patients undergoing any form of advanced airway management versus BVM alone, is appreciably lower than in studies from other areas such as North America (Egly et al., 2011).

3.5.5 Positive association between endotracheal intubation and survival versus supraglottic devices, but negative effect of any advanced airway management versus bag-valve-mask alone – multivariate logistic regression analyses of EMS databases

Two more recent studies have employed registry analyses of large databases with data contributed by multiple EMS agencies across North America to investigate the influence of airway management approach on outcomes in out-of-hospital cardiac arrest. In 2012, the Resuscitation Outcomes Consortium (ROC) found that successful ETI in out-of-hospital cardiac arrest was associated with improvements in both 24-hour survival and survival to discharge with satisfactory functional status when compared with airway management via SGA (Wang et al., 2012). ROC is a research network of Emergency Medical Services (EMS) throughout North America designed to investigate out-of-hospital cardiac arrest (OHCA) and traumatic injury. In this study, Wang and colleagues performed a secondary analysis of clinical data collected prospectively as part of the earlier ROC PRIMED trial (Aufderheide et al., 2011), primarily to determine survival to discharge with satisfactory functional status in adult (≥ 18 years) cases of non-traumatic cardiac arrest managed with endotracheal intubation (ETI) versus insertion of a supraglottic airway (SGA). Satisfactory functional status was defined as a Modified Rankin Scale ≥3. This scale ranges from 0 (no symptoms) to 6 (dead), with a score of 3 indicating moderate disability, where help is required but the patient is able to walk unaided. Secondary outcomes included 24-hour survival, return of spontaneous circulation (ROSC) and presence of airway and pulmonary complications (pulmonary oedema, internal thoracic or abdominal injuries, acute lung injury, sepsis and pneumonia). Patients who did not require advanced airway insertion or in whom these efforts failed were excluded from the analysis. In addition, data from King County and Seattle EMS were excluded as these agencies did not use SGA devices during the study period. Patients receiving both ETI and SGA insertion were classified as SGA cases for the purposes of initial data analysis.

All ROC sites follow uniform data collection methods in accordance with Utstein standards. The ROC includes over 246 EMS agencies, of which 150 contributed to the ROC PRIMED dataset. During the original trial period, 10,455 cases received advanced airway management, of whom 8,487 (81.2%) underwent ETI and 1,968 (18.8%) received SGA insertion. Data on the type of SGA used were available for 1,444 cases and included the King LT (60.3%), Combitube (20.5%), and Laryngeal Mask

Airway (16.6%). The researchers employed multivariable logistic regression to investigate the effect of airway management device on survival to discharge and other secondary outcome measures, controlling for ROC centre, PRIMED trial arm and factors known to influence survival, such as age, gender, bystander or EMS witnessed arrest, bystander CPR, and initial ECG rhythm (shockable versus non-shockable).

Patients undergoing out-of-hospital advanced airway management tended to be older and male. More than half of the OHCAs were bystander or EMS witnessed, and the presenting rhythm was shockable in approximately 25% of cases. Survival to discharge with satisfactory functional status was 4.7% for ETI and 3.9% for SGA. In comparison with successful SGA insertion, ETI was associated with increased survival to discharge with satisfactory functional status (OR 1.40, 95% CI 1.04-1.89), odds of 24-hour survival (OR 1.74, 95% CI 1.49-2.04), and ROSC (OR 1.78, 95% CI 1.54-2.04). ETI was not associated with secondary airway or pulmonary complications (OR 0.84, 95% CI 0.61-1.16). The survival improvement associated with ETI persisted when sites with less than 10% SGA use were excluded and if patients receiving both ETI and SGA insertion were reclassified as ETI rather than SGA cases. However, further data analysis with cases stratified according to six different airway management approaches demonstrated an increased odds of survival associated with absence of ETI or SGA insertion when compared with cases of successful insertion (OR 1.79, 95% CI 1.33-2.40). A model examining the relationship between ETI and the individual SGA devices detected no difference in survival, although it should be noted that data on the specific type of SGA device used were missing for one-third of the 1,968 SGA cases.

In 2014, McMullan and colleagues found similar results when comparing ETI and SGA in their analysis of the Cardiac Arrest Registry to Enhance Survival (CARES) database. In keeping with the ROC database, CARES constitutes a multicentre registry of out-of-hospital cardiac arrests with data reported by in excess of 400 North American EMS agencies. This retrospective review incorporated adult patients aged 18 years and above who underwent resuscitation during 2011 following non-traumatic cardiac arrest of presumed cardiac aetiology. Importantly, the authors also compared outcomes for patients undergoing any form of advanced airway management versus those managed via basic methods alone. During the study period, a total of 12,875 cardiac arrests were reported. Of these, 256 were children and in 83 cases age was unknown. Unlike the ROC registry, data relating to airway management approach is optional in CARES, resulting in the exclusion of a further 1,847 patients. In the remaining 10,691 cases, over 80% underwent some form of advanced airway management, consisting of ETI (n=5,591, 52.6%) or insertion of a SGA (n=3,110, 29.3%). A variety of SGA devices were used, including combitube (n=309, 2.9%), LMA (n=55, 0.5%) and king laryngeal

tube (n=2,746, 25.8%). In a further 61 cases the airway management approach was listed as 'other' and these cases were excluded from further analysis. No successful advanced airway management was performed in 18.2% of cases (n=1,929). In comparison with patients managed via SGA, those undergoing ETI were more likely to be older males presenting in non-shockable rhythms. When compared with cases managed via ETI or SGA insertion, patients managed without an advanced airway intervention were more likely to have experienced an EMS witnessed arrest, present in a shockable rhythm and to have suffered cardiac arrest in a public location or health care facility. Termination of resuscitation occurred significantly less commonly in the ETI group (22.3%) versus the SGA (34.6%) and no advanced airway groups (33.8%). Compared with management via SGA, ETI was independently associated with increased adjusted odds of sustained ROSC (OR 1.35, 95% CI 1.19-1.54), survival to hospital admission (OR 1.36, 95% CI 1.19-1.55), and survival to discharge with good neurological outcome (95% CI 1.44, 95% CI 1.10-1.88). These relationships persisted when adjusting for clinical confounders and propensity score matching. Analysis of cases stratified according to presenting arrest rhythm demonstrated that ETI remained independently associated with increased adjusted odds of hospital survival (OR 2.14, 95% CI 1.39-3.29) and discharge with good neurological outcome (OR 1.94, 95% CI 1.24-3.05) in patients presenting in shockable rhythms only. Compared with those undergoing any form of advanced airway management, patients managed without advanced airway intervention exhibited higher adjusted odds of survival to hospital admission (OR 1.45, 95% CI 1.22-1.72), hospital survival (OR 3.53, 95% CI 2.67-4.66) and discharge with good neurological outcome (OR 4.19, 95% CI 3.09-5.70).

3.5.6 Summary

A relatively large volume of observational studies addressing the influence of airway management on outcomes in out-of-hospital cardiac arrest has been published in recent years. These are drawn from a range of North American and Asian EMS systems with very different operating environments and levels of provider experience and education. Evolving Asian EMS systems provide some opportunity to study the relative contribution of different clinical procedures to outcomes in isolation as interventions such as endotracheal intubation and administration of intravenous drugs are introduced incrementally over time. Sample sizes associated with studies assessing outcomes tend to be larger than those seeking solely to quantify procedural success rates, with some undertaking analyses based on registry data which have established large datasets from international research collaborations. Results from some studies suggest that the aetiology of the arrest may be important in determining the optimal airway management strategy, whereas others report a general trend to improved outcomes with a specific airway device or technique. Of note, some studies suggest that the most favourable outcomes are achieved with bag-valve-mask

ventilation alone, although it is important to note that these cannot control for time to ROSC which may be shorter in patients where escalation to more invasive techniques is not required and is independently associated with improved outcomes (Goto, Funada, & Goto, 2016). Taken as a whole, results from the range of studies discussed above highlight the ongoing uncertainty regarding the true influence of airway management on outcomes in out-of-hospital cardiac arrest and the need for further research.

3.6 Paramedic endotracheal tube misplacement

Although evidence relating to the benefit of ETI in cardiac arrest remains equivocal, unrecognised oesophageal intubation is acknowledged to be an almost universally fatal event in any clinical setting (O'Connor & Swor, 1999). It is therefore important to consider the extent to which tube misplacement and other adverse events may give rise to the apparent association of ETI with the increased mortality observed in some studies addressing prehospital airway management in cardiac arrest. Although prehospital ETI has formed part of resuscitation attempts by selected UK ambulance service personnel since the 1970s (Briggs et al., 1976), no studies have investigated the incidence of unrecognised oesophageal intubation or other adverse events in this setting. In contrast and in the context of a similar history of advanced prehospital airway management (Wang & Yealy, 2006b), several studies addressing complications associated with paramedic ETI have been conducted in the USA.

In 1984, Stewart and colleagues reported data from a prospective observational study to quantify success rates and complications associated with paramedic ETI in the city of Pittsburgh (Stewart et al., 1984). Prior to commencement of the study, 130 paramedics were divided into four distinct groups. The first of these groups consisted of supervisors intended to act as preceptors and record airway management data for the duration of the study. The supervisor group underwent lectures and practical demonstrations of oral intubation techniques in a classroom setting, supported by practice intubating mannequins and pig airways. Each supervisor was then required to perform five successful live intubations under supervision in an operating theatre. Training of the second group mirrored that of the first, whereas the third group was provided with all but operating theatre exposure, and the fourth group was trained using lectures and mannequin practice only. After training, each student was required to successfully complete a skills evaluation by the Service Medical Director prior to being certified to perform ETI under preceptor supervision. Inclusion criteria for the study were patients found in cardiac arrest or in deep coma without intact gag reflex capable of undergoing ETI via direct laryngoscopy. ETI was not permitted in cases of suspected cervical spine injury.

Preceptors observed performance of ETI and prospectively recorded data from May 1980 to July 1982 relating to environmental conditions, clinical presentation, time to intubation, patient outcome and demographics of the paramedic performing the procedure. Successful ETI was defined as placement of the tube in the trachea within 45 seconds measured from ventilation to ventilation. A maximum of three attempts at ETI were permitted. Tube placement was confirmed either at scene if a physician was present or by the receiving ED team using physical examination, direct laryngoscopy or chest X-ray. Complications were defined as prolonged attempts at intubation, teeth, lips or other soft tissue trauma, oesophageal intubation (recognised or unrecognised) and right main stem intubation. Complications were reported by preceptors, physicians at scene or ED staff and verified by the Service Medical Director or EMS physician on call.

ETI was attempted in a total of 883 cases, including 16 patients with potential cervical spine injury who underwent this procedure in violation of established protocol. Patients were excluded from the study if they were found to have an intact gag reflex preventing insertion of the laryngoscope (n=17, 2%), intubated using a special airway guide (n=31, 3.7%), or intubated via a digital (tactile) method (n=10, 1.2%) or nasotracheal approach (n=1, 0.1%). The overall success rate for the remaining 779 patients was 90%. The majority of these patients had suffered non-traumatic cardiac arrest (n=709). Success rates were similar for this group (90.6%) and a group of 33 comatose patients with spontaneous respirations and no evidence of trauma (89.2%). Success rates were lower in patients presenting in either cardiac arrest or deep coma due to trauma (78.8%).

Complications were reported in 9.5% of patients, and included loose teeth (n=3, 0.4%) and oesophageal intubation (n=14, 1.8%). Oesophageal intubation was unrecognised in 0.4% of patients and therefore remained uncorrected. Prolonged intubation attempts (>45 seconds) were noted in 42 patients, 37 of whom were subsequently unable to be intubated. Of the 78 unsuccessful intubations reported during the study, almost half (47.4%) had evidence of prolonged attempts associated with the procedure. Intubation success rates were higher in the first year of data collection, during which only the first and second groups of paramedics were certified in ETI, than in 1981 when all study participants were able to perform the procedure (92.1% versus 86.2%, p=.02). Data from 1982 demonstrated a significant improvement in success rates from the previous year (86.2% versus 94.5%, p=.002).

Although the authors acknowledge that this particular study was not designed to assess the effects of training and experience on ETI success rates, it is noted that a decline in overall success did coincide with the introduction of practitioners with less extensive training and experience. The use of paramedic supervisor preceptors to collect data is arguably a form of peer review that may have

been subject to bias and underreporting of complications. No data is provided on the incidence of complications observed by paramedic preceptors versus physicians at scene or in the ED. The lack of a single uniform method for physician confirmation of tube placement is also a limiting factor, especially given evidence that auscultation alone may be unreliable (Grmec, 2002).

Although other studies have addressed emergency airway management in populations incorporating some patients with prehospital ETI (Jenkins, Verdile, & Paris, 1994; Bozeman, Hexter, Liang, & Kelen, 1996), further studies dedicated solely to paramedic prehospital airway management complications were not conducted until over a decade after Stewart and colleagues published their results (Stewart et al., 1984). At the point at which these studies were conducted, ETI had become regarded as a routine part of USA paramedic practice (Thomas et al., 2007). From 2001 onwards, a series of studies examined the incidence of malpositioned endotracheal tubes and complications associated with the procedure in various paramedic systems within the USA (Katz & Falk, 2001; Jemmett, Kendal, Fourre, & Burton, 2003; Jones et al., 2004; Colwell et al., 2005). The first three of these studies utilised Emergency Department physician verification of tube placement to prospectively determine the incidence of misplaced endotracheal tubes by paramedics in Orange County, Maine, and Indianapolis respectively (Katz & Falk, 2001; Jemmett et al., 2003; Jones et al., 2004). Colwell and colleagues employed a two-phase approach, in which Denver paramedics prospectively completed a closed response data collection instrument to identify number of attempts, methods of confirmation and management of complications in all cases where ETI was attempted. In the second phase of the study, researchers retrospectively reviewed hospital notes to determine airway management complications in patients transported to hospital. In cases where ETI was attempted by paramedics and the patient declared dead in the field, Coroners' records were reviewed to obtain information relating to airway management complications.

All these studies investigated intubation in both trauma and medical cases, and included some comatose patients with a degree of respiratory effort. The latter subset of patients are of limited value in assessing ETI in cardiac arrest, where airway reflexes and sustained respiratory effort are generally absent. With one exception (Jemmett et al., 2003), all studies included intubations attempted via the nasotracheal as well as orotracheal route and none utilised drug assisted intubation. Meta-analysis of prehospital advanced airway management studies demonstrates that success rates are lower and complication rates higher in both ETI attempts in trauma and in all cases where a nasotracheal approach is employed (Hubble, Brown, et al., 2010). These results must therefore be interpreted with caution in the context of airway management in cardiac arrest in the UK, where paramedics only intubate via the orotracheal route. Research was undertaken in a variety

of settings, ranging from systems utilising a tiered response where paramedics only respond to pre-determined categories of call (Katz & Falk, 2001) to those where paramedics routinely respond to all cases (Colwell et al., 2005) and areas with a range of agencies with differing approaches (Jemmett et al., 2003). Jemmett and colleagues noted that higher unrecognised oesophageal intubation rates occurred in rural (12%) and suburban (13%) services than in urban areas (7%), and suggested that caseload and procedural exposure might at least in part constitute an explanation for this variation.

Considerable variation exists between these studies in both the methods employed to verify endotracheal intubation and definitions of a malpositioned ET tube (Table 3). It is therefore difficult to make meaningful comparisons based on overall complication rates. Although it is unlikely that right mainstem bronchus intubation would prove fatal, it would be recorded as a complication in some studies (Jemmett et al., 2003; Colwell et al., 2005) but be considered acceptable in others (Jones et al., 2004). More meaningful comparisons of unrecognised oesophageal intubation rates can be made, given that the definition of this complication is generally universal and appears relatively consistent between these studies. However, the assumption by Colwell et al. that immediate removal of the tube by the ED physician likely constituted an unrecognised oesophageal intubation may have resulted in an erroneous unrecognised oesophageal intubation rate in this study. Indeed, if the one ETI attempt to which this definition was applied without supporting clinical documentation had, in fact, been positioned in the trachea, there would have been a zero unrecognised intubation rate associated with the *orotracheal* approach in this study.

Table 3 Comparison of unrecognised oesophageal intubation rates and confirmation methods in various studies

Study	**Malposition Definitions**	**Physician Confirmation Methods**	**Unrecognised Oesophageal Intubation Rate**
Katz & Falk (2001)	Oesophageal Tube in oesophagus Hypopharyngeal Tube tip above vocal cords	Auscultation chest & epigastrium (extubation if concerns at this stage) Colorimetric or infrared CO2 monitor Laryngoscopy (discretionary)	17% (n=18/108)
Jemmett et al. (2003)	Oesophageal Above the cords Left mainstem Right mainstem	Breath sounds auscultation Infrared CO2 detector Oesophageal detector (discretionary) Laryngoscopy (discretionary) X-ray (discretionary)	9% (n=10/109)
Jones et al. (2004)	Placed outside the trachea	Laryngoscopy Colorimetric CO2 detector Oesophageal detector Physical examination (breath sounds, chest rise, epigastric sounds)	5.8% (n=12/208)
Colwell et al. (2005)	Removal of ET tube by physician in ED (assumed to be oesophageal unless stated otherwise) Oesophageal intubation Broken teeth Hypopharyngeal intubation Epistaxis Pharyngeal laceration Right mainstem intubation Any problem attributed by the hospital team to the out-of-hospital ETI attempt	Not stated *1 malpositioned nasotracheal tube identified on radiograph* *1 orotracheal tube removed immediately but reasons not documented*	0.7% (n=2/278)

Of note, where intubation success rates are quoted in these studies (Table 4), they appear consistent with those reported in studies solely addressing success rates rather than complications. There is therefore a risk that the populations in studies addressing procedural success or influence of airway management strategies on outcome may have been exposed to the range of complications identified above.

Table 4 Intubation success rates in studies examining tube misplacement

Study	**Overall Success Rate**	**Nasal versus Oral Success Rates**
Katz & Falk (2001)	Not given	Not given
Jemmett et al. (2003)	81.4% (n=136/167)	All oral
Jones et al. (2004)	Not given	Not given
Colwell et al. (2005)	84.2% (n=234/278)	Nasal 74% (n= 114/154) Oral 97% (n=120/124)

3.6.1 Summary

There is considerable variation between different studies in the methods both available to EMS providers in the prehospital environment and subsequently used by physicians to confirm endotracheal tube position. The lack of $ETCO_2$ monitoring in the prehospital phase of many studies is likely to be a major contributing factor in the level of tube misplacement identified on arrival at hospital (Silvestri et al., 2005). EMS operating models and clinical guidelines also vary between different study settings, with some providers utilising now largely defunct procedures such as nasotracheal intubation and others permitting attempts at intubation in non-arrest patients with the potential for intact gag reflex. Notwithstanding the fact that these are suboptimal approaches when compared with orotracheal and drug assisted intubation (Hubble, Brown, et al., 2010), they are technically challenging and arguably more prone to tube misplacement. Some systems have noted a decline in intubation success rates over time and note the potential influence of education and procedural exposure on rates of tube misplacement. Although many of these studies included patients with a requirement for advanced airway management in non-arrest scenarios, it is clear that sub-optimal positioning of a tracheal tube has the potential to significantly influence outcome in the context of out-of-hospital cardiac arrest.

3.7 Paramedic endotracheal intubation education and exposure

The level of training for and ongoing exposure to endotracheal intubation are regarded as important factors in determining procedural success rates and clinical outcomes (Jacobs & Grabinsky, 2014). Globally, many different EMS systems exist employing a range of practitioners with varying levels of education and exposure to cardiac arrest and advanced airway management (Lockey, 2009). Two studies from North American EMS systems have investigated the relationship between initial training and exposure to advanced airway management and procedural success rates for student paramedic ETI. In the first, the authors conducted a longitudinal multi-centre review of self-reported intubation and SGA success rates for student paramedics attending one of 60 paramedic training programmes throughout North America during 1999-2003 (Wang, Seitz, Hostler, & Yealy, 2005). The second study investigated self-reported intubation success rates in the Seattle Medic One programme over a 3-year period. This system is characterised by a tiered response, selectively targeting paramedics to high acuity cases, and a comparatively extensive scope of paramedic practice incorporating pharmacologically assisted airway management (Warner et al., 2010).

In both studies, the environment and clinical setting in which attempts at endotracheal intubation were made were recorded. In the study addressing success rates from multiple programmes, these settings were broadly characterised as prehospital, operating room, emergency department, intensive care unit and other hospital locations. Corresponding categories in the Seattle study were operating room, emergency department or prehospital. Neither study specifically reported patient clinical characteristics, although paediatric cases and those undergoing pharmacologically assisted airway management were identifiable in the Seattle study. The Seattle study defined an intubation attempt as any insertion of the laryngoscope into the mouth, whereas there was no a priori definition offered by the authors of the pan North American study. In both studies, successful intubation was presumed to have been verified by the clinical preceptor.

Warner et al. utilised multivariate logistic regression, employing generalised estimating equations with robust variance estimators to assess the effect of cumulative experience on procedural success rates, incorporating cervical spine immobilisation, need for rapid sequence induction and cardiac arrest as potential confounders (Warner et al., 2010). In contrast, Wang et al. utilised fixed effects logistic regression adjusting for multiple covariates, rejecting generalised estimating equations on the basis that this technique produces population rather than subject-specific estimates (Wang et al., 2005). Warner et al. identified a mean first pass rate for Seattle students of 66% and an overall success rate of 88% (Table 5).

Table 5 Cumulative intubation success rates for student paramedics (Warner et al 2010)

Aetiology	Number of cases	First Pass Success	Overall Success
Cardiac Arrest	175	63.4%	88.6%
Trauma	148	63.5%	87.8%
Rapid Sequence Induction	375	67.7%	88.3%

The pooled overall success rate in the pan North American study for students across all programmes was 87.5% (95% CI 86.7-88.2%). First pass success was not reported (Table 6).

Table 6 Pooled intubation success rates for students participating in USA paramedic programmes (Wang et al 2005)

Setting	Success Rate
Overall	87.5% (n=7,635, 95% CI 86.7-88.2%)
Operating Room	89.3% (n=6,311, 95% CI 88.5-90.0%)
Emergency Department	90.0% (n=271, 95% CI 86.4-93.6%)
Intensive Care	68.8% (n=64, 95% CI 57.1-80.4%)
Other Hospital	94.2% (n=86, 95% CI 89.1-99.2%)
Prehospital	74.8% (n=903, 95% CI 71.9-77.6%)

The number of intubations performed by student paramedics varied appreciably, with students from multiple North American programmes exposed to a median 7 intubations (IQR 4-12) compared with 29 (IQR 25-33) for those in Seattle. For Seattle students, the odds of first pass success (OR 1.061, 95% CI 1.014-1.109, p=.009) and overall intubation success (OR 1.097, 95% CI 1.026-1.173, p=.006) increased for each successive patient. Similarly, pooled results for a range of North American programmes demonstrated increased odds of successful intubation associated with cumulative experience (OR 1.067, 95% CI 1.044-1.091). These effects were progressively more pronounced after students were exposed to 10 (OR 1.914, 95% CI 1.534-2.390) 20 (OR 3.664, 95% CI 2.352-5.710) and 30 (OR 7.015, 95% CI 3.607-13.644) intubations respectively. The learning curve for ETI success in this study increased from 77.8% to 95.8% over 30 ETI procedures. Appreciable differences in learning curves were identified between clinical settings, with prehospital ETI exhibiting the 'steepest' curve.

The Seattle training programme trains comparatively low numbers of students in a system characterised by high levels of exposure to clinical procedures (Warner et al., 2010). As a consequence, study results are based on the performance of just 56 students over a period of three years. Conversely, although the pooled success rates from multiple training programmes were based on a much higher number of procedures and students, this analysis only incorporated a total of 891 students drawn from 60 training programmes out of a possible 2,063 students enrolled in 120 programmes (Wang et al., 2005). Results from Seattle students cannot therefore be considered

representative of the entirety of programmes contributing to the database accessed for study purposes and may not be generalizable. Furthermore, these students remotely self-reported airway management success rates via an internet based system, increasing the potential for bias when compared with the Seattle system where it is known that clinical supervisors independently supervised and vetted every intubation attempt. The clinical characteristics of and indications for airway management in patients managed by student paramedics are not reported in either study. It may therefore be that the observed variation in procedural success rates between different environments is representative of the type of patients and scenarios requiring airway management in those areas, rather than the effect of the environment per se. In this instance, clinical environment may simply be a surrogate marker of the clinical complexity encountered by student paramedics. Equally it has been suggested that paramedics may be subject to selection bias in certain environments, whereby the supervising clinician may restrict student paramedic airway management experience to more straightforward or routine cases resulting in artificially inflated success rates (Warner et al., 2010). Finally, a much higher proportion of patients intubated by Seattle student paramedics underwent rapid sequence induction of anaesthesia. This technique is known to increase out-of-hospital airway management success rates in certain patient groups (Davis, Ochs, et al., 2003), but was not available to the student paramedics who contributed the data reviewed by Wang et al.

3.7.1 Summary

National registry requirements for US paramedics mandate a minimum of five intubations prior to graduation (Warner et al., 2010) compared with a historical requirement for 25 successful in-hospital supervised intubations for UK paramedics undergoing traditional in-service technical vocational training (Woollard & Furber, 2010). Pooled results from multiple paramedic programmes suggest that student paramedics are likely to require exposure to in excess of 25 intubation attempts to achieve overall success rates above 90% in a range of clinical settings (Wang et al., 2005). Warner et al. examined both first pass and overall intubation attempts and found that the learning curve was steepest specifically for prehospital airway management. In this setting, overall intubation success rates plateaued after 15 prehospital attempts but no such plateau was observed in the learning curve for first pass success, leading the authors to conclude that in excess of 20 prehospital attempts may be required to produce acceptable first pass success rates. First pass success may be especially important in the context of cardiac arrest, where repeated intubation attempts have been demonstrated to correlate with interruptions in chest compressions in one North American study (Wang, Simeone, Weaver, & Callaway, 2009). Overall, these studies demonstrate the effects that system and training factors may have on intubation success rates in paramedic systems, albeit

exclusively in the North American setting. It is therefore plausible that these factors may at least in part account for some of the variation in clinical outcomes reported in a range of studies addressing advanced airway management in cardiac arrest.

3.8 Effect of procedural experience on outcome

The studies discussed above have analysed the effect of ETI stratified by presenting cardiac arrest rhythm and apparent aetiology, but have not examined the effect of procedural experience on outcomes. Review of other studies suggests that considerable variation exists between different EMS systems in the numbers of practitioners trained to perform ETI and the provision of airway management training and exposure to the technique. In an attempt to investigate the effect of procedural experience on outcomes in patients undergoing ETI, Wang et al. retrospectively analysed airway management data collated from the Pennsylvania Emergency Medical Services Care Report Database, Pennsylvania Health Care Cost Containment Council, and the Pennsylvania Death Registry (Wang et al., 2010). Paramedics perform the majority of out-of-hospital intubations (94%) in Pennsylvania, although out-of-hospital nurses and physicians also perform ETI, predominantly as part of aeromedical teams. These providers are also permitted to perform RSI, whilst a small number of selected ground based paramedics are authorised to use sedation-only drug assisted intubation.

The authors obtained data relating to patients undergoing successful out-of-hospital ETI via the Pennsylvania Emergency Medical Services Care Report Database for the period January 2003 to December 2005. ETI success is self-reported as part of a written or electronic care record completed by the provider performing the procedure, with no provision made for recording unsuccessful ETI attempts. Investigators searched the Emergency Medical Services Care Report Database from 2000 to 2002 to establish the number of intubations performed by each rescuer prior to the study period and the cumulative ETI experience of the rescuer for each ETI performed during the study period. The number of cumulative patient contacts of any type was also calculated for individual practitioners from January 2000 to the date of the intubation under consideration to provide a marker of previous general clinical experience. Where the data set attributed ETI to more than one clinician, the clinician with the highest level of cumulative ETI experience was used for the purposes of multivariate analysis. Where two clinicians had the same ETI experience, the clinician with the highest number of patient contacts was used.

Given that the three databases did not share a unique patient identifier for each case where ETI was performed, Wang et al. utilised probabilistic linkage to connect patient records. This methodology has been employed in other medical studies, and compares values from a variety of data fields, such

as date, time, and gender, to estimate the probability that pairs of records match (Woodward, 2014). The primary outcome measure was survival to discharge, as determined from the Pennsylvania Death Registry and Health Care Cost Containment Council records. Patients with cardiac arrest, medical non-arrest, and major trauma were analysed separately in view of the differing prognoses and airway management approaches associated with each. Patients who received chest compressions or defibrillation, or presented in ventricular fibrillation, ventricular tachycardia, pulseless electrical activity or asystole were classified as having suffered cardiac arrest. All other patients were classified as non-arrest cases. The Pennsylvania Emergency Medical Services Care Report Database does not include any standard measures of injury acuity, therefore the investigators used a priori incident classifications, such as stabbing, and known predictors of serious injury, such as fall >20 feet, to identify patients with potential major trauma. This database also makes no provision for recording whether ETI was performed as part of an RSI or sedation facilitated procedure, therefore the investigators were unable to adjust for cases involving pharmacologically assisted airway management.

During 2003-2005, 4,846 practitioners undertook ETI, performing the procedure on 33,117 patients. During 2000-2005 median practitioner experience was 10 intubations (IQR 4-19). A priori definitions of very high (>50), high (26-50), medium (11-25), and low (1-10) experience levels were defined based on this data. Multivariate analyses adjusting for patient demographics, Utstein variables and key EMS timings were performed to calculate adjusted odds of survival with practitioner experience as the key independent variable. In the context of cardiac arrest, adjusted odds of survival were higher for patients intubated by practitioners with very high versus low tracheal intubation experience (OR 1.48, 95% CI 1.15-1.89). Corresponding values were not statistically significant for high (OR 1.13, 95% CI 0.98-1.31) and medium experience levels (OR 1.02, 95% CI 0.91-1.15). In 8,162 medical nonarrests, adjusted odds of survival were higher for patients intubated by rescuers with high (OR 1.29, 95% CI 1.04-1.59) and very high (OR 1.55, 95% CI 1.08-2.22) tracheal intubation experience. Practitioner experience was not significantly associated with survival in 3,202 trauma nonarrests.

3.8.1 Summary

Although results suggest that higher cumulative practitioner experience with the procedure of endotracheal intubation is associated with improved odds of survival in cardiac arrest, this study has a number of limitations. Although intubation in cardiac arrest can generally be accomplished without pharmacological adjuncts, patients not in cardiac arrest may exhibit intact airway reflexes and require sedation and/or paralysis to facilitate passage of an endotracheal tube. Procedural

success rates in such circumstances are in part dependent upon the availability of such agents and, where these are available, whether sedation only, neuromuscular blockade only, or full rapid sequence induction (RSI) of anaesthesia combining both drug classes is available to the provider (Hubble, Brown, et al., 2010). In this study, the researchers were unable to determine cases where RSI was employed, yet this procedure is established to provide significantly higher success rates than other forms of drug or non-drug assisted intubation (Hubble, Brown, et al., 2010). Despite these limitations, the study offers additional insight beyond other research in establishing the effects of education and exposure on procedural success rates to describe a potential causal link between experience and survival in cardiac arrest. This may constitute an important potential confounder in out-of-hospital cardiac arrest research addressing the influence of various airway management approaches on survival and neurological outcome.

3.9 Alternative airway devices - procedural success rates

In 2008, the UK Joint Royal Colleges Ambulance Liaison Committee Airway Working Group report recommended that the majority of prehospital airway management should focus on the use of SGA devices rather than ETI (Deakin, Clarke, et al., 2010). Following this recommendation, two snapshot retrospective audits evaluating the introduction of the i-gel SGA were undertaken within a UK ambulance service (Duckett, Fell, Han, Kimber, & Taylor, 2013). Ambulance patient report forms relating to cases of adult cardiac arrest where active resuscitation was undertaken during May 2011 and January 2012 were reviewed by a paramedic researcher to determine the method of airway management, procedural success rates, and any documented adverse events.

During the initial audit phase a total of 76 cases were identified with adequate information to determine the airway management approach available for 69 patients. During the subsequent audit in January 2012 a total of 134 cases were identified with complete data available for 116. In 2011 the overall airway management success rates were 94% (n=33) for i-gel and 86% (n=25) for ETI. Corresponding values in 2012 were 92% (n=58) and 90% (n=37) respectively. The authors note that a minority of staff experienced difficulty in inserting the i-gel, although this is not quantified further. The use of retrospective audit methodology to review a snapshot of data drawn from one month periods over two successive years limits the extent to which these results can be generalised to the service in which this work was undertaken, let alone the wider UK EMS system. The rationale for the choice of these two particular time periods is also unclear but may be important given evidence of temporal variation in cardiac arrest aetiology and outcome (Brooks et al., 2010).

As the use of SGA devices has become more commonplace within EMS systems globally, a number of prospective observational studies have investigated their use in the management of out-of-hospital

cardiac arrest. In 2008, Hein and colleagues undertook a prospective observational audit following the introduction of a first generation LMA into the South Australian Ambulance Service (Hein, Owen, & Plummer, 2008). Two further European studies employing prospective observational approaches investigated use of the LMA Supreme and i-gel SGA devices amongst nurse-paramedics in the Netherlands (Bosch et al., 2013) and paramedics and physicians in Germany (Haske, Schempf, Gaier, & Niederberger, 2013) respectively. Finally, Chien et al. report results following the introduction of the Intubating LMA to an evolving EMS system in Taiwan where no advanced airway management had previously been undertaken in the prehospital phase of treatment (Chien et al., 2012).

Hein et al. (2008) identified 179 attempts at LMA insertion in 164 patients by a range of volunteer ambulance staff, student paramedics, paramedics and intensive care paramedics within the South Australian Ambulance Service. In 85% (n=139) of cases the patient presented in cardiac arrest. In the remaining cases the patient was unconscious. Overall procedural success rate was 74%, with successful insertion in 45% of patients on the first attempt and a further 20% on the second attempt. The remaining patients required between three and six attempts before the LMA was inserted successfully. Paramedics self-reported reasons for failure as patient anatomy (n=13), technique (n=9), airway soiling (n=7), device complications (n=6), trismus (n=1), conscious level (n=1), trauma (n=1) and unknown (n=5). Logistic regression analysis did not demonstrate a significant relationship between overall success rates and the number of times a practitioner had been exposed to the procedure in the preceding 12-months (p=.17). These results contrast with those achieved by Dutch nurse-paramedics using the LMA supreme in a series of 50 patients (Bosch et al., 2013), who achieved 100% successful insertion and a 98% first attempt success rate. Three attempts were required in the single remaining patient, although the reasons for this are not reported. Ventilation via the LMA supreme was possible in the majority of cases (98%, n=49). In the remaining cases, one patient recovered rapidly rendering SGA insertion unnecessary and the other was intubated by a prehospital doctor. Similarly, Haske et al. (2013) reported that German paramedics and physicians achieved a 100% overall success rate using the i-Gel SGA in a series of 70 cases of prehospital cardiac arrest. In 90% of cases successful insertion was achieved on the first attempt, with a further 7% achieved after two attempts and the remainder within three attempts. In 80% (n=56) of these cases the practitioner was able to ventilate the patient without noting any air leak. In a further 17% (n=12) a moderate air leak was noted, and in 3% (n=2) of cases ventilation was not possible due to major air leak. The authors note a significant relationship between ability to site the device and subsequent difficulties with ventilation (r=0.99, p=.02). Absence of air leak was sufficient to enable continuous compressions in 74% (n=52) of cases. Despite this, 46% (n=32) of patients underwent ETI at some stage after i-gel insertion. Of note, results from the European studies reporting comparatively high

insertion success rates suggest that the ability to insert an SGA does not necessarily correlate with adequate ventilation, although the specific difficulties encountered by practitioners in cases of inadequate ventilation are not reported.

Despite methodological similarities, the study of I-LMA use by Tawainese Emergency Medical Technicians did not report procedural success rates, rather the authors sought to investigate the introduction of a SGA device in a system previously limited to bag-valve-mask valve ventilation in cardiac arrest. Although the I-LMA is a SGA device with a specially designed port to permit passage of an endotracheal tube following insertion, the investigators did not permit ETI during the study period and selected this device on the basis that the rigidity of the I-LMA would be of particular value in the intended patient population. During September 2004 and June 2005, a total of 113 patients were ventilated with BVM and from July 2005 until June 2007 a total of 332 patients were ventilated via i-gel following the introduction of the device after a mannequin based training programme. A total of 24 BVM and 23 i-gel cases were excluded due to incomplete data. In the remaining cases, the authors compared patient demographics, time at scene, arterial blood gases and ROSC between the two groups. In comparison with BVM cases, patients undergoing i-gel insertion had longer mean scene times (9.5 minutes versus 4.8 minutes, p=.006) and higher rates of ROSC (47.6% versus 36.4%, p=.05) and 24-hour survival (36.2% versus 24.7%, 95% CI 0.01-0.22, p=.043). Laboratory values did not differ significantly between the groups. Although the absence of data relating to number of attempts at insertion and subsequent ventilation failure rates limits the extent to which these results can be generalised or compared with results from other prospective observational studies, the authors conclude that the I-LMA proved to be an efficient and effective means of providing airway management in an evolving EMS system.

As the availability and range of SGA devices for prehospital resuscitation has expanded, other authors have sought to compare procedural success rates and other clinical data between different products. A randomised controlled trial conducted within the same South Australian ambulance service previously reporting relatively low LMA procedural success rates (Hein et al., 2008) compared outcomes between the LMA device used in the original study and the i-gel in patients aged 12 and above presenting in cardiac arrest (Middleton, Simpson, Thomas, & Bendall, 2014). In contrast to the previous study, participants were qualified paramedics only, with other providers such as volunteers and intensive care paramedics excluded from participation. The study was conducted in response areas served by six stations not staffed by intensive care paramedics. Study paramedics were provided with equipment to undertake both LMA and i-gel insertion, with randomisation achieved by the study paramedic opening a sealed study envelope directing them to

the appropriate arm of the trial. Paramedics were provided with mannequin based training in the use of the i-gel but no further training in the use of the LMA as this was regarded as an established skill within this system. A maximum of two attempts to insert the SGA were permitted, after which practitioners were instructed to revert to basic airway management.

On the basis of the previous procedural success rate of 64% identified in this system, the authors determined that 50 patients per trial arm would be required to detect a clinically important difference. Given the frequency of cardiac arrests in this service, a trial period of 12-months was thought to be sufficient to achieve the desired sample size. However, despite extending the study beyond 12-months until the stage at which the i-gel expiry dates were reached, recruitment proceeded at a slower rate than anticipated and only 51 patients in total were recruited. A total of 163 cardiac arrests occurred during the trial, with 62 eligible patients not enrolled. Reasons for non-enrolment were presence of intensive care paramedics (n=26), absence of trial paramedic (n=21), failure to transport study kit to patient (n=6), arrest witnessed by paramedic (n=4), lone working (n=2) and unknown (n=3). A total of 51 patients were subsequently randomised, three of whom were not in cardiac arrest at the time at which the SGA was inserted and were therefore excluded from further analysis. Patients were randomised to management via LMA in 28 cases and i-gel in the remaining 20. Successful insertion was achieved in 57% (n=16) of LMA cases and 90% (n=18) of i-gel cases (p=.023). Paramedics rated ease of insertion on a scale from 1 (very easy) to 5 (very difficult). Significantly lower median ease of insertion scores were reported for the i-gel (2 versus 3, p=.001), whereas no significant differences were noted in the number of attempts required to insert the device and rates of ROSC.

The relatively low levels of procedural success associated with LMA use in this study (57%) appear broadly consistent with those observed in the previous study conducted in this setting (64%), particularly given that participants in this study were restricted to two attempts to achieve SGA insertion whereas those in the preceding study took up to 6 attempts in some cases. The authors postulate that differences in device design, notably the absence of a requirement to inflate the laryngeal cuff, may explain the relatively higher success rates associated with the i-gel. Equally further training prior to study commencement was provided solely for the i-gel on the assumption that LMA insertion was already an established skill and this may have skewed results in favour of this device. Further limitations associated with this study include failure to achieve the target sample size and lack of assessment of ventilatory adequacy post insertion.

Most recently, the REVIVE-Airways feasibility study (Benger et al., 2016) compared two types of second generation SGA with standard UK paramedic airway management in non-traumatic cardiac

arrest. The study employed cluster randomisation methodology and was conducted in a single UK ambulance service comprising urban and semi-rural patient populations (Benger et al., 2013). Paramedics who volunteered to participate in the study were randomly allocated to one of three trial groups to either use the i-gel or LMA Supreme SGA device as the first line advanced airway in cardiac arrest, or to continue with standard practice incorporating bag-valve-mask ventilation, insertion of a standard first generation LMA and ETI at the discretion of the paramedic. Paramedics randomised to the i-gel or LMA Supreme arms were issued with a personal supply of the relevant device. The primary outcome measure was successful ventilation, defined as visible chest movement with each ventilation. Secondary outcomes included insertion success, ROSC, survival to hospital discharge and neurological status assessed via the CPC score. In survivors, further neurological assessment in the form of the Cambridge Neuropsychological Test Automated Battery (CANTAB), Delayed Matching to Samples (DMS), Depression Anxiety and Stress Scale (DASS) and SF-36 Health Survey tests was undertaken.

Study paramedics received an additional 2 hours of structured training consisting of 60 minutes of generic training and an additional 50 minutes of training specific to the study arm to which they had been allocated. During the study period, paramedics were instructed to follow standard UK resuscitation council procedures and to then proceed with airway management according to the trial arm as dictated by the first study paramedic to arrive at scene. A maximum of three attempts to establish an advanced airway of no longer than 30-seconds duration each were permitted. In the event that successful airway placement as per the trial arm had not been achieved within three attempts, the paramedics were instructed to institute whichever form of airway management was felt to be appropriate for the clinical situation at their discretion. Of note, subsequent analysis was undertaken on an intention to treat basis. Of 535 eligible paramedics, a total of 184 (35%) consented to participate. The number of eligible patients attended by each paramedic during the 12-month study period ranged from 0 to 11, with 9% of participants not attending any out-of-hospital cardiac arrests during this time. A total of 232 (38%) patients were managed via the i-gel device, with 174 (28%) undergoing LMA Supreme insertion and the remaining 209 (34%) randomised to standard care. The LMA Supreme was discontinued after 10 months due to three reports of practitioner contamination via the gastric drainage port incorporated as part of this device. First attempt placement success for the i-gel was 79%, with practitioners unable to insert the device in 4% of cases and inadequate ventilation reported in a further 17%. Corresponding values for the LMA Supreme were 75% first attempt success with an inability to insert the device in 4% of cases and inadequate ventilation in a further 21%. ETI was attempted in 267 patients (46%) with a first pass

success rate of 85%. There was no statistically significant variation in ROSC, admission to hospital, survival to hospital discharge or neurocognitive and quality of life measures.

As a feasibility study, the REVIVE-Airways trial was not sufficiently powered to detect clinically significant differences in outcome between the three airway management approaches. However, the authors report that contamination resulting from use of the LMA supreme led to declining confidence in and eventual withdrawal of this device. Although not statistically significant, admission to hospital, survival to hospital discharge and 90 day survival were lowest in the LMA supreme group (Table 7).

Table 7 Comparison of clinical outcomes between the three trial arms of the REVIVE-Airways study (Benger et al 2016)

Outcome	**I-Gel**	**LMA Supreme**	**Standard Practice**
ROSC at hospital	30.8% (70/227)	31.2% (53/170)	32.7% (67/205)
Admission to hospital	22.0% (50/227)	17.6% (30/170)	21.0% (43/205)
Survival to discharge	10.3% (24/232)	8.0% (14/174)	9.1% (19/209)
Survival to 90 days	9.5% (22/232)	6.9% (12/174)	8.6% (18/209)

Failures in the form of inability to insert the device or inadequate ventilation post insertion occurred in a total of 21% of i-gel and 25% of LMA supreme cases. In clinical terms, use of an SGA in this study initially resulted in inadequate airway management or ventilation in between one in four and one in five patients. These findings are broadly consistent with the incidence of air leaks impeding ventilation identified as moderate in 17% and major in 3% of patients managed by paramedics and physicians in a German EMS system using the i-gel device (Haske et al., 2013). However, the adverse events and relatively low first attempt success rates associated with the LMA Supreme contrast with those reported in a study of Dutch Nurse-Paramedics, where use of the LMA Supreme following failed intubation or as a primary airway in unconscious patients was associated with 98% first pass success and an overall 100% success rate in a cohort of 50 patients, although study participants did report air leakage in 14% of these cases (Bosch et al., 2013). Employing intention to treat methodology may also have skewed the results in favour of devices requiring fewer attempts to achieve insertion or described as easier to insert, as repeated attempts to establish an advanced airway have been linked to worsened outcomes in some studies relating to out-of-hospital cardiac arrest.

In keeping with comparative analysis of clinical evidence from emergency medical systems globally, the studies considered here demonstrate considerable heterogeneity in terms of geographical setting, system design and maturity, and level of practitioner education and experience. In some studies SGA devices are used predominantly by less skilled providers operating as part of a tiered

response system (Hein et al., 2008; Middleton et al., 2014) or as rescue devices following failed intubation attempts (Haske et al., 2013). In others, they constitute the sole means of advanced airway management in the prehospital setting (Chien et al., 2012). Practitioner experience with advanced airway management varies considerably, with certain studies reporting on the introduction of SGA devices as alternatives to ETI in established EMS systems and others reviewing results following the implementation of SGAs in settings where EMS systems remain in their infancy. There is also considerable variation between these studies in the level of provider education and legal and regulatory frameworks for practice. Some report results from systems with established higher education for paramedics and high levels of individual autonomy (Hein et al., 2008; Middleton et al., 2014), whereas in other settings regulatory constraints do not permit fully autonomous practice and on-line medical control is a common feature (Chien et al., 2012).

3.9.1 Summary

The level of heterogeneity in studies addressing SGA use is perhaps more pronounced than that observed in studies examining endotracheal intubation, not least because the range of SGAs now available is relatively extensive (Ostermayer & Gausche-Hill, 2014). This contrasts with the technique of endotracheal intubation and the equipment required to achieve this, which has remained largely unchanged except for the introduction of video laryngoscopy which is not widespread within most EMS systems (Niforopoulou, Pantazopoulos, Demestiha, Koudouna, & Xanthos, 2010). Despite the apparent advantages associated with SGA devices, including lower training requirements and less adverse events (Deakin, Clarke, et al., 2010), no single SGA has emerged as a universal alternative to ETI in out-of-hospital cardiopulmonary resuscitation. Results from some studies suggest that certain SGA devices will fail to provide adequate ventilation in as many as one in four patients in cardiac arrest (Haske et al., 2013; Benger et al., 2016). Both the UK REVIVE-Airways study (Benger et al., 2013) and randomised controlled trial conducted in South Australia (Middleton et al., 2014) identified that certain SGA devices may be more prone to adverse events or failure in out-of-hospital resuscitation, therefore the specific device used in individual studies is an important consideration when comparing results. Nonetheless, collectively the results from these studies provide some reassurance that various forms of first and second generation SGA devices can and do have a role in airway management in cardiac arrest as part of a range of interventions.

3.10 Meta analyses of studies addressing out-of-hospital airway management in cardiac arrest

With the increasing volume and breadth of studies addressing out-of-hospital airway management, the literature is now sufficiently developed to support systematic review and meta-analysis. In 2010, Jensen and colleagues conducted a systematic review comparing ETI with alternative airway techniques by paramedics but elected not to perform meta-analysis due to study heterogeneity (Jensen, Cheung, Tallon, & Travers, 2010). In the same year, Hubble et al. published results from two large scale meta-analyses of tracheal intubation (Hubble, Brown, et al., 2010) and alternative airway success rates (Hubble, Wilfong, et al., 2010) for all prehospital practitioners. All authors incorporated adult and paediatric patients with a range of medical and traumatic presentations and, in the case of Hubble et al., included some studies where drug assisted airway management was performed. As the debate regarding the optimal method of airway management in out-of-hospital cardiac arrest has gathered momentum, more recent meta-analyses have addressed outcomes for adult patients managed with advanced airway interventions versus basic methods alone in cardiac arrest of any aetiology (Fouche et al., 2014) and ETI versus SGA in non-traumatic cardiac arrest (Benoit, Gerecht, Steuerwald, & McMullan, 2015).

The first meta-analysis conducted by Hubble et al. provided pooled estimates of success rates for orotracheal and nasotracheal intubation following systematic literature searches of all English language studies reporting success rates for any prehospital provider globally (Hubble, Brown, et al., 2010). In the second meta-analysis, the authors employed the same methodology to identify literature and pooled success rates for alternative airway devices, incorporating a range of extra and supraglottic airways as well as surgical and needle cricothyroidotomy (Hubble, Wilfong, et al., 2010). In both instances, titles of potential studies were reviewed by two reviewers and excluded if both were in agreement regarding lack of relevance. In the second phase, two reviewers assessed abstracts and excluded studies where both agreed lack of relevance. In the final stage, two authors scrutinised full papers for the remaining studies, with discrepancies in decisions resolved by consensus. Inter-relater reliability was assessed at each stage via the kappa statistic. Quality assessment of individual studies was undertaken via an assessment tool designed by the authors on the basis that most established quality assessment tools for meta-analyses are designed for evaluation of randomised controlled trials and little or no such studies currently exist in prehospital care. Data were extracted relating to route of intubation or type of device used, patient demographics, indication for airway management, pharmacological adjuncts used to facilitate airway management where applicable, professional background of the practitioner, environment in which procedures were performed, methods for verifying device placement, and whether the procedure

was performed as a primary intervention or rescue procedure following failed attempts using other methods. Paediatric patients were defined a priori as those aged 12 years or below. The primary outcome variable was the pooled proportion of successful procedures for each airway device or approach. The proportion of successful placements was defined as the number of patients in whom an advanced airway was successfully established divided by the number in whom the procedure was attempted. Subgroup analyses were planned where sufficient information was available to identify patient groups with specific characteristics, such as those treated by a specific provider or where studies addressed specific aetiologies such as trauma. Heterogeneity was assessed via the Cochrane Q test and I^2 statistic with publication bias evaluated using funnel plots and the Egger regression test.

A total of 2,005 studies were identified as potentially relevant to both meta-analyses, with 140 studies included in the first meta-analysis addressing orotracheal (n=117) and nasotracheal (n=23) intubation with a combined total of 54,933 patients. A further 46 studies were included in the second meta-analysis, of which 35 addressed alternative airway devices and the remaining 21 reported results relevant to needle or surgical cricothyroidotomy. Studies addressing alternative airway devices yielded a combined patient population of 10,172, with a further 512 patients in whom cricothyroidotomy was attempted. No randomised controlled trials were identified, and the majority of included studies employed observational methodology. More than a third of the selected studies were retrospective in nature and some were more than 30 years old at the time at which the meta-analysis was conducted. Pooled estimates for procedural success rates associated with individual devices and techniques are shown below (Table 8).

Table 8 Pooled estimates for procedural success rates associated with alternative airway devices (Hubble, Wilfong et al 2010)

Airway Approach	**Pooled Estimate**	**95% Confidence Interval**
Orotracheal intubation – all non-drug assisted	86.3%	82.6-89.4%
Orotracheal intubation – cardiac arrest	91.2%	83.6-92.2%
Orotracheal intubation – sedation facilitated	86.8%	80.2-91.4%
Orotracheal intubation – rapid sequence induction	96.7%	94.7-98.0%
Nasotracheal intubation	75.9%	65.9-83.7%
Esophageal obturator airway	92.6%	90.1-94.5%
Pharyngotracheal lumen airway	82.1%	74.0-88.0%
Oesophageal-Tracheal Combitube	85.4%	77.3-91.0%
Laryngeal Mask Airway	87.4%	79.0-92.8%
King Laryngeal Tube Airway	96.5%	71.2-99.7%
Needle Cricothyroidotomy	65.8%	42.3-83.6%
Surgical Cricothyroidotomy	90.5%	84.8-94.2%

Substantial heterogeneity was identified in studies addressing the oesophageal obturator airway (Q statistic $\chi^2 = 21.36$, p=.08, $I^2 = 62.5\%$) oesophageal-tracheal Combitube (Q statistic $\chi^2 = 359$, p=.000, $I^2 = 95.0\%$), laryngeal mask airway (Q statistic $\chi^2 = 172.71$, p=.000, $I^2 = 93.6\%$), King laryngeal tube (Q statistic $\chi^2 = 7.52$, p=.023, $I^2 = 73.4\%$), orotracheal intubation (Q statistic $\chi^2 = 3,151$, p<.001, $I^2 = 95.1\%$) and nasotracheal intubation (Q statistic $\chi^2 = 131.47$, p<.001, $I^2 = 82.5\%$). Minimal heterogeneity was identified for studies addressing needle cricothyroidotomy (Q statistic $\chi^2 = 3.49$, p=.321, $I^2 = 14.1\%$) and no assessment of heterogeneity was undertaken for the pharyngotracheal lumen airway as only one study was included.

A further systematic review conducted in 2010 sought to identify randomised, quasi-randomised or observational studies comparing paramedic ETI with alternative airway strategies of any type, including bag-valve-mask ventilation with basic airway adjuncts as well as extraglottic devices (Jensen et al., 2010). Studies involving paediatric patients were eligible for inclusion, but those where clinicians other than paramedics performed some or all of the airway interventions were excluded. Although the authors initially identified 4,434 studies and reviewed a total of 257 abstracts, the more specific and methodologically stringent selection criteria employed resulted in the inclusion of five studies involving 1,559 patients following the review process. The only randomised controlled trial included compared basic airway management with ETI in children. The remaining studies involved adult patients in cardiac or respiratory arrest from a range of aetiologies. In keeping with the approach adopted by Hubble and colleagues (Hubble, Brown, et al., 2010; Hubble, Wilfong, et al., 2010), the authors assessed heterogeneity via the I^2 statistic and Breslow-Day χ^2 test with significance set at $p < .10$. Although the results of these analyses are not provided, the authors determined that the level of heterogeneity was such that pooling results via meta-analysis was inappropriate. None of the studies reviewed demonstrated any significant differences in procedural success rates, survival to admission and incidence of good neurological outcome between ETI and alternative airway management methods.

More recent meta-analyses of airway management in cardiac arrest have addressed outcomes for patients managed with any form of advanced airway management versus basic methods alone (Fouche et al., 2014) and ETI versus SGA devices (Benoit et al., 2015). The initial intention of Fouche et al. was to select studies exclusively comparing advanced airway interventions with basic methods incorporating nasopharyngeal and oropharyngeal airway adjuncts where applicable in adult patients with non-traumatic out-of-hospital cardiac arrest. However, this approach failed to yield a sufficient number of studies, therefore the inclusion criteria were expanded to incorporate traumatic cardiac arrests and patients of all ages. The authors excluded studies reporting neurological outcome

measures beyond one month on the basis that these studies would not accurately reflect outcome relating to the episode of cardiac arrest. Three reviewers assessed abstracts and then reviewed selected studies for inclusion. Two further reviewers subsequently assessed methodological quality and potential for bias via an adapted checklist. The main outcome measures were return of spontaneous circulation and survival to hospital admission (short term survival) and hospital discharge and neurological status at one month (long term survival). Due to the range of SGAs used in the included studies no analysis of individual devices was undertaken. However, sub group analysis of outcomes stratified according to whether ETI was performed or any form of SGA inserted was undertaken. The literature search identified 799 articles, of which 90 were identified for further assessment. Of these, a total of 19 studies were including in the final analysis. There was high inter-rater agreement between assessors (0.90, 95% CI 0.74-0.96) and the mean quality score was 0.59 (95% CI 0.50-0.67). Five studies with the highest ratings were conducted in East Asian EMS systems during 2010-2013. The majority of studies assessed as lower quality were conducted before 2000 in European and North American EMS. There was no significant difference in short term survival between advanced airway and basic management (OR 0.84, 95% CI 0.62-1.13) and a non-significant decrease in the odds of ROSC associated with advanced airway use (OR 0.78, 95% CI 0.60-1.02). Advanced airway management was associated with a non-significant increase in odds of hospital admission (OR 1.40, 95% CI 0.83-2.37) and a significant decrease in the incidence of good neurological outcome specifically at one month (OR 0.41, 95% CI 0.28-0.60) and all indicators of long term survival in general (OR 0.49, 95% CI 0.37-0.65). Sub group analysis of the ETI group identified a non-significant trend towards decreased short term survival (OR 0.79, 95% CI 0.54-1.16) and a significant decrease in long term survival (OR 0.48, 95% CI 0.36-0.64). Similarly, use of SGA devices was associated with significantly decreased odds of short (OR 0.56, 95% CI 0.40-0.78) and longer term survival (OR 0.35, 95% CI 0.28-0.44).

In contrast, Benoit and colleagues identified sufficient studies for meta-analysis of outcomes for adult patients treated with either ETI or SGA devices in exclusively non-traumatic out-of-hospital cardiac arrest (Benoit et al., 2015). Studies where providers other than paramedics were responsible for airway management were excluded, as were those where pharmacologically assisted airway management techniques, video laryngoscopy or now obsolete SGA devices such as the oesophageal obturator were used. The results of this meta-analysis therefore arguably correspond most closely to the context in and indications for which UK paramedics most commonly perform advanced airway management. Two researchers sequentially reviewed titles, abstracts and full text articles, excluding studies at each stage that did not meet the established inclusion criteria. Final decisions on the inclusion of articles were made via a consensus process involving the entire research team. A total

of 3,454 titles and 325 abstracts were reviewed, with 10 studies ultimately selected for inclusion. The main outcome measures were ROSC, survival to hospital admission, survival to hospital discharge and neurologically intact survival as determined by Cerebral Performance Category (CPC), Modified Rankin Scale or Glasgow Outcome Scale. Quality of studies was assessed via the GRADE rating system and heterogeneity via Cochrane's Q test and corresponding I^2.

The ten selected studies all employed observational methodology and encompassed a total of 34,533 ETI and 41,116 SGA patients. Although the authors assert that baseline clinical characteristics were broadly similar between study populations, no measures of difference were applied and the proportion of patients presenting in a shockable rhythm ranged from 7.5% to 29% between individual studies. Compared with those managed via SGA devices, patients who underwent ETI had significantly higher odds of ROSC (OR 1.28, 95% CI 1.05-1.55), survival to hospital admission (OR 1.34, 95% CI 1.03-1.75), and neurologically intact survival to hospital discharge (OR 1.33, 95% CI 1.09-1.61) and a non-significant trend towards improved survival to hospital discharge (OR 1.15, 95% CI 0.97-1.37). Significant heterogeneity was present amongst the included studies for ROSC (I^2=85.4%, p<.001) and survival to hospital admission (I^2 85.4%, p<.001) but not for survival to hospital discharge (I^2=48.8%, p=.068) or neurologically intact survival (I^2=20.2%, p=.28). The majority of studies were considered of low or very low quality, predominantly due to inadequate adjusting for confounders known to affect survival from cardiac arrest. Further analyses performed following exclusion of very low grade evidence demonstrated that ETI remained associated with higher odds of neurologically intact survival (OR 1.33, CI 1.04-1.69). The authors conclude that although effect sizes are relatively small, the association of ETI with improved clinical outcomes persisted despite multiple analyses of different combinations of studies. In addition, the oldest study included in this analysis was published in 2007, therefore these results are likely to provide a reasonable reflection of contemporary practice.

The processes of systematic review and meta-analysis are intended to identify all relevant studies in a given area and employ explicit methods of statistical analysis to combine data in order to provide pooled estimates of the effectiveness of a given intervention (Moore & McQuay, 2006). The QUOROM statement on publication of systematic reviews provides guidance on key aspects of quality assessment, including literature review methods, study selection processes, grading of quality and bias (Turpin, 2005). Application of these guidelines to the systematic reviews and meta-analyses discussed above highlights several inconsistencies rendering meaningful comparison of pooled estimates between individual meta-analyses problematic. Good quality meta-analyses of randomised controlled trials are often regarded as the most reliable offerings in evidence-based

practice (Moore & McQuay, 2006), however the majority of studies included in meta-analyses of airway management in cardiac arrest are observational in nature thus limiting the statistical validity of this research. These difficulties are highlighted in the systematic review conducted by Jensen et al. where the authors determined that meta-analysis was inappropriate due to the degree of variation in systems and operating procedures between the various EMS agencies in which research had been conducted (Jensen et al., 2010). The only RCT identified in this systematic review related to the use of ETI in paediatric patients, where the aetiology of presentations requiring advanced airway management differs from that seen in adult populations (Writer, 2007) and therefore is of limited relevance to the management of adult cardiac arrest patients.

Arguably the most comprehensive review of out-of-hospital airway management was undertaken by Hubble and colleagues. However, the broad nature of the inclusion criteria employed by the researchers resulted in a plethora of data drawn from a variety of systems and countries employing a range of practitioners with differing levels of skill and expertise utilising multiple airway management devices, techniques, procedures and, in some cases, pharmacological regimens in both medical and trauma patients (Hubble, Brown, et al., 2010; Hubble, Wilfong, et al., 2010). Some of the studies included in these reviews are more than 30 years old, during which time there have been multiple developments and changes in resuscitation and airway management guidelines, including a de-emphasis of the role of tracheal intubation (Daya et al., 2015) and a clear preference for the use of rapid sequence induction of anaesthesia as the preferred approach to pharmacologically assisted prehospital airway management (Bernard, 2006; Bernard, Nguyen, et al., 2010). In addition, a number of the alternative supra and extraglottic airway devices incorporated in this analysis are now obsolete. Other confounding factors include the influence of practitioner education, experience, professional background and exposure to airway management, although the authors did conduct sub-group analyses to address these concerns. A key finding from this review was the degree of variation in procedural success rates between different SGA devices given that these are often considered as a whole rather than individually in most other meta-analyses.

The only meta-analysis to compare basic methods of airway management versus advanced interventions in the form of any SGA device and ETI found that clinical outcomes were poorer in patients exposed to any form of advanced airway management (Fouche et al., 2014). Again, this analysis ultimately incorporated cardiac arrest from medical and traumatic causes in patients of any age after insufficient studies were identified when inclusion criteria were limited to cases of adult non-traumatic arrests. The ability to perform advanced airway management in injured patients without pharmacological adjuncts has been shown to correlate with poor outcomes (Lockey, Davies,

& Coats, 2001) and is therefore likely to have had an appreciable effect on pooled results. In addition, a degree of confounding by indication may be present in these results given that escalation to advanced airway management may be more likely to occur in prolonged resuscitation or clinically challenging cases that are more likely to have worse outcomes. Time to ROSC has been shown to be a significant predictor of survival (Komatsu et al., 2013). It may therefore be that those patients managed via basic methods alone achieved ROSC more rapidly, however individual studies did not report this data. Finally, the authors note the difficulties in comparing outcome data between individual studies, given the range of measures of short and long term outcomes used. This resulted in exclusion of studies reporting outcome data beyond 30-days post discharge, despite evidence from other airway management studies that much longer follow up periods may be required to comprehensively assess long term neurological outcome following out-of-hospital advanced airway management (Bernard, Nguyen, et al., 2010).

In contrast, Benoit et al. compared outcomes between management solely by paramedics via SGA and ETI in non-traumatic cardiac arrest but did not consider patients managed via basic methods alone. Studies incorporating older now obsolete SGA devices were excluded but the relatively limited pool of studies selected meant that cases managed via SGA were again grouped together for the purposes of meta-analysis despite evidence of appreciable variation in procedural success rates between individual devices (Hubble, Wilfong, et al., 2010; Benger et al., 2016). The oldest study included in this review was published in 2007, therefore the evidence incorporated in this analysis is arguably more contemporary than that included in other meta-analyses. However, the authors acknowledge that this resulted in some aspects of the analysis being dominated by studies from Asia where EMS systems are nascent and indications for and the availability of prehospital advanced airway management differ from more established systems in other countries (Trevithick et al., 2003; Pozner et al., 2004; Black & Davies, 2005; Lockey, 2009).

3.10.1 Summary

Although a number of researchers now consider that there exists an adequate volume of studies relating to out-of-hospital airway management in cardiac arrest to facilitate systematic review, there is no universal agreement that these studies are collectively sufficiently homogenous to permit meta-analysis. Considerable heterogeneity exists in terms of aetiology, patient characteristics, practitioner type, and operating system to the extent that some authors of systematic reviews addressing out-of-hospital airway management assert that any form of meta-analysis in this area is inappropriate. Overall, there exists considerable tension between identifying individual study populations which are collectively sufficiently homogenous to permit comparison versus ensuring an adequate sample size to permit meaningful statistical analysis and pooling of results. It therefore

follows that where meta-analyses have been published, these should be interpreted with caution given the issues identified above.

3.11 Overall Summary

Airway management is a core component of prehospital care, yet significant scientific equipoise remains regarding the most appropriate approach in out-of-hospital cardiac arrest. An increasing body of literature now exists in this area, developing over time from retrospective reviews with often small sample sizes to larger prospective observational studies addressing procedural success rates and factors affecting performance such as experience and education. More recent studies remain largely observational but have progressed to assessing the impact of airway management approach on survival and neurological outcome rather than simply quantifying procedural success. A number of these are based on registry data generated from largescale research collaborations which are reliant upon data submission from multiple individual services. Several meta-analyses have been undertaken to pool results from multiple studies, however many have encountered challenges arising from the considerable heterogeneity present within EMS systems internationally and variation in population demographics and inclusion and exclusion criteria. Some evidence suggests that factors such as aetiology, presenting rhythm and timing or sequencing of advanced airway procedures may be important factors in influencing outcomes. Despite the optimism accompanying the increasing introduction of a range of supraglottic devices, findings suggest that these are by no means a panacea for airway management in prehospital care and that procedural success rates may vary according to the specific device in use. Although the optimal airway management approach remains unknown, it is clear that practitioner education and exposure and EMS operating model significantly influence procedural success rates and therefore potentially clinical outcomes.

3.12 Implications for the current study

The above literature review serves to highlight the heterogenous nature of studies addressing out-of-hospital airway management both generally and in the specific context of cardiac arrest. At the outset, the intention was to acquire an in-depth understanding of a range of approaches to out-of-hospital airway management research, highlighting the relative merits and potential pitfalls associated with different studies to inform the design of and provide a rationale for the subsequent methodological approach and data collection process. A general theme identified during review of the literature is the tension between achieving an adequate sample size to facilitate statistical analysis versus ensuring a sufficiently clinically homogenous sample to permit meaningful comparisons between sub-groups within individual studies and results from other studies. This is

highlighted in findings reported from some meta-analyses, where the level of heterogeneity resulting from factors such as EMS operating model, aetiology, sample demographics and clinical management approach renders pooled analysis of results problematic. This equally applies to analyses of cardiac arrest registry data contributed by multiple sites across geographical boundaries.

Historically, out-of-hospital airway management research has progressed along a continuum from early retrospective approaches characterised by small sample sizes designed to quantify procedural success rates and provide relatively unsophisticated outcome measures such as ROSC to prospective observational studies providing longitudinal follow up permitting the application of more sophisticated outcome measures incorporating neurological and functional status. Although the volume of studies is now perceived by some to be sufficient to permit meta-analysis, there remain a number of specific patient groups whose needs have received little or no research attention in terms of the influence of airway management strategy on outcome. Patients diagnosed with STEMI and transferred directly to a specialist HAC are a clear example of this. Although appreciable efforts have been directed at quantifying clinical outcomes and defining populations likely to benefit most from direct transfer to such centres, no studies have specifically examined how prehospital airway management strategy may influence outcome regardless of the interventions provided after hospital arrival. In contrast to the heterogenous nature of the resuscitation populations from which existing study samples are often drawn, patients accessing HAC services after ROSC in the prehospital phase constitute a relatively homogenous population which may have significant benefits in terms of adjustment for confounding where observational research approaches are employed. In addition, many of the challenges reported in previous research relating to follow up may be ameliorated in the context of a regionalised system of care within specialist centres with established relationships and data reporting arrangements with EMS agencies with whom they collaborate.

4. Predictors of survival in out-of-hospital cardiac arrest

4.1 Introduction

The preceding literature review highlights the challenges associated with accounting for confounding factors in airway management research and the need to develop methodological approaches which ensure that an appropriate range of clinical and demographic variables are incorporated into study datasets. Appreciable resources may be required to collect clinical and demographic data. It is therefore vital that data collection approaches are based on a sound rationale derived from a comprehensive understanding of the evidence base. Developing an understanding of and accounting for confounding variables affecting survival are key aspects of determining the optimal airway management approach in out-of-hospital cardiac arrest. Multiple factors relating to both patient and clinical demographics as well as EMS operating model and hospital after-care have the potential to influence survival regardless of airway management approach. This section reviews the evidence for factors influencing survival and neurological outcomes in out-of-hospital cardiac arrest through critical analysis of systematic reviews, meta-analyses, survival modelling and studies examining both multiple survival predictors and specific individual variables. These findings will guide and inform methodological approaches and the structure of the study dataset.

4.2 Systematic and meta-analyses of survival predictors

The most recent systematic analysis and meta-analysis of predictors of survival from out-of-hospital cardiac arrest incorporated thirty years of data, attempting to account for variation in EMS system, regional survival rates and location (Sasson, Rogers, Dahl, & Kellermann, 2010). Furthermore, the authors sought to investigate underpinning evidence relating to resuscitation decision making rules based on established predictors of survival (Verbeek et al., 2002; Morrison, Visentin, Kiss, Theriault, Eby, Vermeulen, Sherbino, Allan, et al., 2006; Morrison, Visentin, Kiss, Theriault, Eby, Vermeulen, Sherbino, & Verbeek, 2006; Morrison, Verbeek, et al., 2007; Morrison, Visentin, et al., 2007; Morrison, Bigham, Kiss, & Verbeek, 2008; Morrison, Verbeek, Zhan, Kiss, & Allan, 2009). All studies addressing survival from out-of-hospital cardiac arrest from 1950-2008 were considered for inclusion. Studies reporting solely in-hospital cardiac arrest outcomes, those with predominantly non-cardiac aetiology (trauma, drowning, electrocution, respiratory), and those containing >20% paediatric cases were excluded.

A total of 204 studies were evaluated, of which 79 were selected for meta-analysis. The included studies ranged from 1984-2008 and all employed observational cohort methodology. Collectively the studies reported outcomes for 142,740 patients. The pooled rate of survival to discharge was 7.6% (95% CI 6.7-8.4). Where studies reported survival to hospital admission (n=49), the pooled rate

was 23.4% (95% CI 20.7-26.1). Studies reporting arrests witnessed by bystanders versus unwitnessed (n=36) demonstrated pooled odds of survival to discharge of 0.34 (95% CI 0.07-1.66) among those with the highest baseline survival rates to 4.42 (95% CI 1.81-10.80) in those with the lowest baseline survival rates. Thirty-two studies reported on the association of bystander CPR with survival, yielding pooled odds of survival for those undergoing CPR of 1.23 (95% CI 0.71-2.11) in studies with the highest baseline survival rates to 5.01 (95% CI 2.57-9.78) in those with the lowest baseline survival rates. A larger number of studies reported data relating to the presence of a shockable rhythm (VF/VT), with pooled odds of survival ranging from 2.91 (95% CI 1.10-7.66) to 20.62 (95% CI 12.61-33.72) in studies with the lowest and highest baseline survival respectively. Only 12 studies reported data on the relationship between ROSC and subsequent outcomes, with considerable variation in definition of ROSC between individual studies ranging from any return of a palpable pulse to sustained ROSC and the presence of a palpable pulse on leaving scene. Excluding one study incorporating ROSC at hospital in outcome measures reduced pooled odds of survival from 99.84 (95% CI 14.30-696.89) to 35.29 (95% CI 5.54-224.94). Regression analyses demonstrated that the type of EMS system accounted significantly for heterogeneity in odds of survival for shockable rhythms ($p<.05$). The largest pooled odds ratio was evident at locations where a public access defibrillator was available (OR 12.5) and the smallest at sites where both basic and advanced life support were provided (OR 5.1). Variation in case-mix resulting from differences in the proportions of patients with cardiac versus non-cardiac aetiologies and length of follow up ranging from discharge to one month also accounted for significant variation in odds of survival. Performance of Begg's test for publication did not reveal significant evidence of publication bias ($p >.05$).

Overall, findings from meta-analysis indicate that survival is higher amongst patients who receive bystander CPR and are found in a shockable rhythm. The association between shockable rhythm and survival was greatest in locations with access to a community defibrillator. The provision of bystander CPR delays the degradation of a shockable rhythm, which may explain the significance of this intervention (Herlitz et al., 1994). The most powerful predictor of survival was found to be ROSC during the prehospital phase of treatment, although this is likely a surrogate marker for other aspects of what is now commonly referred to as the chain of survival, such as bystander CPR (Perkins et al., 2015). In systems characterised by lower baseline survival rates, the magnitude of effect sizes for variables such as bystander CPR and presence of a shockable rhythm were much higher than in systems with higher baseline survival. This appears broadly consistent with experiences in the OPALS study, which found limited incremental improvements in outcome from further expansion of

clinical scope of practice in an EMS system already optimised to achieve rapid defibrillation (Stiell et al., 2004).

4.2.1 Summary

Common predictors of survival from out-of-hospital cardiac arrest are now largely known and agreed internationally, however research continues to be limited by challenges associated with accurate data recording in the prehospital phase of treatment and variation in EMS systems globally (Chamberlain, 2010). These differences may impact upon decisions to commence or terminate resuscitation, the type of personnel undertaking resuscitation, treatments available in the prehospital phase and post ROSC care depending on geographical location (Adnet & Lapostolle, 2004; Gomes, Araujo, Soares-Oliveira, & Pereira, 2004; Langhelle et al., 2004; Papaspyrou et al., 2004; Pozner et al., 2004; Symons & Shuster, 2004; Black & Davies, 2005; MacFarlane et al., 2005; Weninger, Hertz, & Mauritz, 2005). Although this may limit the generalisability of some findings and render meta-analyses of data problematic (Moore & McQuay, 2006), it is of paramount importance that established predictors of survival are both understood and challenged in order to optimise future resuscitation strategies (Chamberlain, 2010).

4.3 UK studies examining multiple predictors of survival

More recently, two UK based observational studies have examined predictors of outcome following out-of-hospital cardiac arrest. Whittaker and colleagues conducted a retrospective review of case notes and national databases where Percutaneous Coronary Intervention (PCI) was performed for patients who presented to a single ED following out-of-hospital cardiac arrest from 2008-2013 (Whittaker et al., 2016). Outcome measures were sustained ROSC and survival to hospital discharge. In a further single-centre, prospective observational study, researchers from the Harefield Cardiac Arrest Study investigated predictors of outcomes in patients transferred directly to a specialist Heart Attack Centre (HAC) with ROSC following out-of-hospital cardiac arrest (Iqbal et al., 2015). Importantly, this study analysed functional status at discharge graded via the modified Rankin Scale (mRS) and all-cause mortality at 30 days and 1 year. This scale ranges from 0 (no significant disability) to 6 (dead), with mRS 0-3 considered indicative of favourable functional status (Rittenberger, Raina, Holm, Kim, & Callaway, 2011). Both studies undertook statistical testing using the Mann Whitney U Test and Chi-square or *Z* test for categorical variables respectively, progressing to stepwise logistic regression analysis to determine predictors of survival for prehospital and in-hospital models.

Whittaker et al. (2016) identified a total of 350 cardiac arrest patients transferred by EMS to the ED during the study period, with sustained ROSC (>20 minutes) achieved in 56% (n=196) of cases. Of

these, 58.2% (n=114) survived to hospital discharge. A cardiac cause was identified in three quarters of patients (n=262, 75%) and 40% (n=140) underwent immediate coronary angiography. Non-cardiac causes included respiratory arrest, metabolic disorders, haemorrhage and brain injury. Median age was significantly higher in non-survivors versus those who survived to hospital discharge (72.0 versus 59.5 years, p<.001). An ECG was recorded in 99% (n=195) of patients who achieved ROSC, with ST segment elevation identified in 56% (n=109) of cases. Odds of survival to discharge were significantly higher in patients with versus without ST elevation on the post ROSC ECG (OR 3.5, 95% CI 1.9-4.6). In the cohort of patients who achieved ROSC, regression analysis demonstrated that non-shockable rhythm (OR 5.5, 95% CI 1.34-22.5), absence of bystander CPR (OR 3.0, 95% CI 1.30-8.5), downtime > 15 minutes (OR 2.5, 95% CI 1.1-5.7) and initial pH ≤7.11 (OR 5.6, 95% CI 2.0-15.4) were significant predictors of in-hospital death. Unwitnessed cardiac arrest and absence of ST elevation were not significant predictors of outcome.

The Harefield Cardiac Arrest investigators prospectively reviewed outcomes for 174 patients transferred directly to a single HAC, with good versus poor outcomes dichotomised as mRS 0-3 and mRS 4-6 respectively. In keeping with results from the ED study (Whittaker et al., 2016), higher proportions of patients with good neurological outcomes presented in a shockable rhythm (92.6% versus 70.9%, p<0.001). Median duration of resuscitation, expressed as downtime in the ED study, was significantly shorter in patients with good (4 minutes) versus poor outcome (16 minutes, p<.001). Proportions of patients with witnessed cardiac arrest did not differ, however significantly more patients with good outcomes suffered cardiac arrest in the presence of EMS (48.4% versus 17.7%, p<.001). Proportions of patients with ST elevation did not differ significantly between outcome groups, however direct transfer to a HAC within this EMS system mandates the presence of ST elevation or a limited range of ECG patterns associated with acute coronary syndrome (Fothergill, Watson, Virdi, Moore, & Whitbread, 2014). Rates of adrenaline administration and advanced airway management were significantly higher in the cohort with poor outcomes (p<.001). Results from logistic regression analysis demonstrated that cardiogenic shock (HR 2.46, 95% CI 1.37-4.43, p=.03), duration of resuscitation (HR 1.03, 95% CI 1.01-1.05, p<.001) and advanced airway use (HR 6.67, 95% CI 2.66-16.74, p<.001) were predictors of 30-day mortality. These factors were also significant predictors of one-year survival with the addition of Charleson Comorbidity Index score (HR 1.16, 95% CI 1.04-1.31, p=.010).

Appreciable differences exist between the ED and HAC study populations, although both were undertaken within EMS and hospital systems within London and the South of England and therefore findings are arguably more generalisable to the UK than many of the European and North American

data incorporated in previous meta-analyses. Outcome measures incorporating functional outcomes and long-term survival were comparatively more sophisticated in the Harefield study, however the population consisted exclusively of patients with evidence of ST segment elevation or other signs of ACS (Iqbal et al., 2015) and therefore might reasonably be expected to have better outcomes than the more general resuscitation population included in the ED study (Fothergill et al., 2014), a quarter of whom did not have evidence of cardiac aetiology (Whittaker et al., 2016). Findings that shockable rhythm and witnessed arrest were significantly associated with improved outcomes are consistent with existing literature (Sasson et al., 2010; Dumas & Rea, 2012; Mader et al., 2012), although the Harefield investigators only identified arrests specifically witnessed by EMS as significant whereas Whittaker et al. (2016) did not investigate this sub-group. It is therefore possible that the proportion of EMS witnessed arrests is an important confounder within the resuscitation literature where this is not reported separately. The observation of higher rates of advanced airway management and adrenaline administration in the cohort with poor outcomes in the Harefield study may be subject to significant confounding, given that both are likely surrogate markers for prolonged resuscitation attempts on the basis of the sequencing of interventions in current guidelines (Soar et al., 2015) and that time to ROSC has been shown to be an independent predictor of survival (Goto et al., 2016).

4.3.1 Summary

Findings from the comparatively limited UK-specific literature are broadly consistent with predictors of survival identified in international research. This provides a degree of reassurance that findings from other countries with differing health economies and EMS systems are still of relevance in informing study design and data collection methods. Collectively, the UK studies comprise patients with predominantly cardiac aetiology and are therefore of particular interest. Interestingly, witnessed cardiac arrest was not a significant predictor of survival in either UK study. However, it must be acknowledged that these samples were derived solely from patients who were transferred to the HAC or ED and therefore cannot be used to determine the effect of bystander CPR on out-of-hospital mortality. This is an important distinction to highlight when analysing study results and in determining a priori inclusion and exclusion criteria.

4.4 Models of survival

As predictors of survival following out-of-hospital cardiac arrest have become more established and better understood, researchers have sought to develop models to account for complexities and relationships in outcome data and optimise survival within various EMS systems. Fridman and colleagues conducted survival modelling for urban and rural EMS based on the Victorian Ambulance

Cardiac Arrest Register (VACAR) for cases during 2002-2005 (Fridman et al., 2007). Primary endpoints were survival to discharge and presence of a shockable rhythm. Multivariate regression analyses were conducted to investigate the relationship between primary outcome measures and clinical variables selected on the basis of Utstein reporting guidelines. Logistic analysis was restricted to adult (≥ 15 years) patients with witnessed cardiac arrest of presumed cardiac aetiology. Piecewise regression was used for the continuous variables age and response time. During the study period a total of 18,827 patients suffered out-of-hospital cardiac arrest, with resuscitation attempted in 43.5% of cases. The main analysis performed in cases of witnessed arrest of presumed cardiac aetiology (n=3,506) demonstrated higher proportions of survivors in cases presenting in a shockable versus non-shockable rhythm (15.7% versus 3.7%) and where bystander CPR was performed (12.0% versus 7.6%). In a logistic regression model of survival to discharge, age >60 years (OR 0.96, 95% CI 0.95-0.98) and male gender (OR 0.73, 95% CI 0.54-0.99) were associated with reduced odds of survival, whereas the presence of a shockable rhythm (OR 2.53, 95% CI 1.2-5.36) and performance of bystander CPR in patients presenting in a shockable rhythm (OR 2.07, 95% CI 1.3-3.30) were associated with increased odds of survival to discharge. Age, gender, response time, public location and bystander CPR were also significant predictors of the presence of VF.

Further survival models based on North American data were subsequently developed in Los Angeles (Kaji, Hanif, Bosson, Ostermayer, & Niemann, 2014), Boston (Abrams, Moyer, & Dyer, 2011) and via the Cardiac Arrest Registry to Enhance Survival (CARES) database (Abrams, McNally, Ong, Moyer, & Dyer, 2013). Abrams et al. (2011) and Kaji et al. (2014) undertook modelling based on Boston EMS registry and Harbor-UCLA hospital data, incorporating cases from 2004-2007 and 2008-2013 respectively. Although the Boston EMS registry is a purpose designed cardiac arrest data repository, investigators in the Harbor UCLA study were required to abstract data from a variety of sources including EMS run sheets, ED notes and hospital clinical records (Kaji et al., 2014). Both studies included adult (≥ 18 years) out-of-hospital cardiac arrests of presumed cardiac origin. Abrams et al. (2011) included all eligible cases where resuscitation was attempted by EMS (n=1,168) whereas Kaji et al. (2014) only included patients who survived to hospital admission from the ED (n=184). Boston EMS registry data (Abrams et al., 2011) were analysed via multivariate logistic regression to develop two survival models based on survival to discharge and the presence of shockable rhythm coupled with prehospital ROSC as opposed to Kaji et al. (2014) who employed Classification and Regression Tree (CART) analysis to review factors predictive of survival with good (GCS 14&15) versus poor (GCS <14) neurological outcome.

The overall survival rate for eligible cases from the Boston EMS registry was 11.1%. Higher rates of survival to hospital discharge were observed in younger (p<.001) male (p=.002) cases that were witnessed (p<.001), presented in a shockable rhythm (p<.001), achieved prehospital ROSC (p<.001), occurred in a public place (p<.001), had bystander CPR (p<.001), and Boston EMS response times for BLS (p=.04) and ALS (p=.005) resources of less than four minutes. For patients presenting in non-shockable rhythms, survival to discharge rates were 0.3% in the cohort without prehospital ROSC (n=577) versus 8.7% in those who achieved ROSC prior to ED arrival (n=173, p<.001). Corresponding figures for cases found in a shockable rhythm were 1.7% without prehospital ROSC (n=181) versus 54.3% in those with ROSC (n=199, p<.001). Multivariate analysis demonstrated that odds of survival were significantly increased in the presence of ROSC in the prehospital setting (OR 13.1, 95% CI 4.6-37.7) and a composite of ROSC and shockable rhythm (OR 8.2, 95% CI 4.3-15.8). Survival odds were also increased in cardiac arrests that were witnessed (OR 2.7, 95% CI 1.3-5.4), occurred in a public place (OR 2.1, 95% CI .12-3.7) and received shorter (<4 minutes) EMS response times (OR 2.1, 95% CI 1.2-3.6). A non-significant trend (p=.06) towards increased survival was noted in cases exposed to bystander CPR (OR 1.7, 95% CI 1.0-3.0). Older age (>80 years) was associated with reduced odds of survival (OR 0.3, 95% CI 0.1-0.9). A second multivariate model consisting solely of patients presenting in a shockable rhythm who achieved prehospital ROSC demonstrated that witnessed arrests (OR 5.6, 95% CI 3.7-8.7) in public places (OR 2.2, 95% CI 1.5-3.2) with bystander CPR (OR 2.3, 95% CI 1.6-3.3) and shorter response times (OR 1.7, 95% CI 1.2-2.5) continued to be associated with increased odds of survival, whereas older age remained predictive of lower odds of survival (OR 0.5, 95% CI 0.3-0.9). The authors highlight the importance of the presence of a shockable rhythm and prehospital ROSC, noting that although approximately 18% of the study sample presented with a composite of shockable rhythm and prehospital ROSC, this sub-group comprised around 84% of those who survived to discharge.

Similarly, univariate analysis by Kaji et al. (2014) of the smaller sample of ED patients demonstrated that younger age (median 59 versus 65 years, p=.03), shockable rhythm (70% versus 26%, p<.0001), witnessed arrest (88% versus 73%, p=.04) and bystander CPR (61% versus 42%, p=.03) were predictive of good outcome (GCS ≥14). Shorter time to ROSC (median 17.5 minutes versus 23 minutes, p<.0001) and lower adrenaline doses (median 1mg versus 2mg, p<.0001) were also more prevalent in survivors with good neurological outcome. Patients who received adrenaline had longer times to ROSC and were less likely to have a witnessed arrest, receive bystander CPR, present in a shockable rhythm or survive to discharge. The only significant predictor associated with good neurological outcome in adjusted analysis was the presence of a shockable rhythm (OR 3.7, 95% CI 1.4-10, p=.01).

In contrast to database analyses confined to single EMS systems or individual hospitals, survival modelling undertaken by Abrams et al. (2014) incorporated data contributed to the CARES registry from over 400 EMS agencies and 900 hospitals within North America (McNally et al., 2011). Inclusion criteria were out-of-hospital cardiac arrest with presumed cardiac aetiology that occurred during 2005-2011. Cases where cardiac arrest occurred after EMS arrival were excluded (n=5,048). A total of 25,975 cases were included in survival modelling, although response times were missing in 15,502 of these as this field is optional within the CARES database. There were no variables such as travel distance that could be used as surrogate markers of response time, however cohorts with versus without response time data were judged to be comparable in terms of predictors of survival. Two survival analysis models were developed. The first incorporated cases that presented in a shockable rhythm and achieved prehospital ROSC. The second model investigated the direct effects of predictor variables on outcomes in the sub group with a composite of shockable rhythm and prehospital ROSC. The authors assert that individual predictors may have both direct effects on survival and indirect effects via their impact on the probability of shockable rhythm with prehospital ROSC occurring. The two multivariate regression equations were estimated separately for all cases combined and three sub-groups consisting of bystander witnessed cases, unwitnessed cases and bystander witnessed shockable cases.

Univariate analysis demonstrated that 59% of cases (n=15,426) were unwitnessed and less than a quarter (23.5%, n=6,104) presented in a shockable rhythm. Logistic regression analysis revealed that in witnessed cases bystander CPR, shorter response time (<4 minutes) and public access AED use had statistically significant direct effects on survival and indirect effects via their association with the presence of the composite of shockable rhythm and prehospital ROSC. In contrast, in unwitnessed cases, bystander CPR and shorter response time (<4 minutes) had no direct or indirect effects, whereas use of public access AED had a direct but not indirect effect on survival. In a second phase of analysis, application of regression equations to sample data facilitated the development of projections for survival rate increases under various scenarios. If all cases were exposed to bystander CPR and shorter response times (<4 minutes) overall survival was predicted to rise from 9% to 12%. Application of a public access AED to all cases was predicted to increase survival from 9% to 14%. Exposure of all witnessed arrests to bystander CPR and shorter response times led to a projected improvement in survival rates from 16% to 23% and from 16% to 29% with public access AED use. For unwitnessed cases, bystander CPR and shorter response times had no significant direct or indirect influence on survival. However public access AED use was associated with a projected survival improvement from 4% to 6%. The authors conclude that model predictions indicate that bystander CPR and shorter response times have a significant impact on survival for witnessed but

not unwitnessed cases, whereas public access AED use has a positive impact for all cases but this is less pronounced where the arrest is unwitnessed.

Despite the considerable variation between individual studies modelling outcomes in out-of-hospital cardiac arrest, common predictors of survival such as witnessed cardiac arrest and the presence of a shockable rhythm (Sasson et al., 2010) remained consistently associated with improved odds of survival across a range of populations and associated sub-groups. Taken as whole, the various survival models incorporated data from Australian and North American EMS systems and hospitals for cases occurring during the period 2002-2013. Substantial heterogeneity exists between these studies in terms of hospital and EMS systems (Trevithick et al., 2003; Pozner et al., 2004; Lockey, 2009), geographical considerations, methodological approach and sampling procedures. A number of resuscitation guideline changes would also have occurred during some data collection periods, which may have been responsible for variations in treatment approaches and potentially survival outcomes (Kudenchuk et al., 2012).

The majority of studies used multivariate regression analysis (Fridman et al., 2007; Abrams et al., 2011; Abrams et al., 2013), however Kaji et al. (2014) employed a regression tree analysis (CART) approach. Classification and regression trees partition samples into distinct sub-sets in order to estimate the predicted probability of the event of interest occurring (Lemon, Roy, Clark, Friedmann, & Rakowski, 2003). Critics of the CART approach assert that regression trees are reliant on partitioning samples using binary decision rules, thus losing the ability to incorporate linear relationships (Austin, Tu, & Lee, 2010). Studies comparing CART with conventional logistic regression approaches to model in-hospital survival in heart failure and myocardial infarction report higher predictive accuracy with logistic regression methodology (Austin, 2007; Austin et al., 2010). In addition, the substantial proportion of cases with missing response time data (n=15,502) in the CARES analysis is a potential confounder. The reasons for this are unclear, however response time is a core component of reporting as per international Utstein standards (Perkins et al., 2015), therefore the potential for agencies with poor performance in this area to withhold data cannot be ignored. The CARES analysis was the only study to examine the influence of public access defibrillation on survival, with predictive analysis suggesting that the largest survival gains with expansion of bystander AED use would be in the sub-group with witnessed cardiac arrest and bystander CPR. This experience accords with evaluations of UK public access AED schemes, which identify highly significant survival advantages associated with the use of an AED prior to EMS arrival in witnessed out-of-hospital arrests with bystander CPR (Colquhoun et al., 2008) alongside ongoing challenges in improving access to pre-arrival defibrillation (Deakin, Shewry, & Gray, 2014).

4.4.1 Summary

Although the process of survival modelling may be used to identify potential areas for system modification to improve survival, it also highlights the complexities associated with accounting for the myriad of factors that influence clinical outcomes in out-of-hospital cardiac arrest. Individual studies employ a variety of methodological approaches, however most are characterised by some form of multivariate regression analysis and the calculation of adjusted odds ratios. Data sources in many also correspond with those available via the host EMS system and participating HACs. Common challenges include dealing with missing data and ensuring consistent reporting of time related measures in the prehospital phase. These will therefore be important considerations in the development of the study methodology and standardised data set.

4.5 Age as a predictor of survival

Two recent retrospective observational studies specifically investigated the influence of age on outcomes following out-of-hospital cardiac arrest. Terman and colleagues conducted a retrospective review of Michigan University ED health records for patients coded as presenting with non-traumatic out-of-hospital cardiac arrest during 2005-2012, excluding those aged less than 18 years (Terman, Shields, Hume, & Silbergleit, 2015). A total of 638 adult patients underwent treatment in the ED following out-of-hospital cardiac arrest, of whom 48 were excluded due to traumatic aetiology. Outcome measures included discharge and long term (6-12 month) CPC, Charlson Comorbidity Index (CCI) and Charlson-age index. The CCI was originally developed to assess mortality risk amongst in-hospital general medical patients, and underwent validation in surgical and oncology patient cohorts. It provides a summed score based on severity-weighted points for chronic health conditions (Charlson, Pompei, Ales, & MacKenzie, 1987). Data analysis incorporated Chi-square testing and logistic regression modelling CPC dichotomised as favourable (CPC1&2) or unfavourable (CPC3-5) as the outcome. In a second study, researchers conducted a retrospective review of the Swedish CPR register, which now incorporates national data relating to more than 90% of out-of-hospital cardiac arrests where EMS attempted resuscitation (Libungan et al., 2015). The study included patients aged 70 years and older who suffered cardiac arrest during 1990-2013. Primary outcome measures were survival and 30-day outcome assessed via CPC, with statistical analyses incorporating Mann-Whitney U testing, Spearman's rank correlation and logistic regression with reporting of associated adjusted odds ratios. A total of 36,605 patients were identified and stratified into age ranges consisting of those aged 70-79 (53%), 80-89 (40%) and ≥90 (7%).

Despite differing EMS systems, sample sizes, and population age ranges, both studies reported that increasing age was associated with higher mortality. Terman et al. (2015) identified that increasing decade of life was associated with poorer neurological outcome in both an unadjusted model (OR 0.78, 95% CI 0.70-0.88) and when adjusting for CCI alone (OR 0.80, 95% CI 0.71-0.90). In a fully adjusted model, neither CCI (OR 1, 95% CI 0.87-1.2) nor combined Charlson-age index (OR 0.9, 95% CI 0.82-1.0) were significant predictors of outcome. Similarly, Libungan et al. (2015) found that 30-day survival reduced from 6.7% in those aged 70-79 years, to 4.4% in the 80-89 age group and 2.4% in those aged 90 and over ($p<.0001$). Further analyses of these data stratified in six year periods from 1992 onwards demonstrated an overall increase in survival but that the association of increasing age with mortality persisted. This provides valuable information in terms of the potential confounding effects of resuscitation guideline changes on outcomes over time (Kudenchuk et al., 2012).

Terman et al. found that in their ED setting, decade of life was associated with increased odds of withdrawal of care (OR 1.2, 95% CI 1.1-1.3), thus highlighting the potential influence of institutional and clinical decision making behaviours on outcomes in older patients. Both studies identified increasing age was associated with an increase in the prevalence of female patients and a decrease in the proportions of those presenting in a shockable rhythm. Terman et al. found that age was a stronger predictor of survival in those presenting in a shockable rhythm, suggesting that age may have a greater influence on outcome in sub-sets of patients with a higher baseline probability of survival. Equally the presenting rhythm may reflect differing aetiologies (Dumas & Rea, 2012). Libungan et al. also found that bystander CPR was highest in the oldest age group. Although the reasons for this are unclear, it may relate to patients living in residential facilities such as nursing homes where immediate trained assistance might reasonably be expected to be routinely available.

Importantly, the distribution of CPC scores amongst 30 day survivors in the Swedish study did not vary significantly, highlighting that although increasing age is associated with higher mortality, survival with good neurological outcome is not uncommon in older patients. In contrast to the other patient groups, there were no 30-day survivors in the cohort aged 90 years and over with a CPC score >2. These findings should be interpreted with caution given that the proportion of cases in each cohort for whom complete neurological outcome data were available ranged from 42-45% (Libungan et al., 2015). Although no further exploratory analysis is provided, this may reflect a greater readiness to withdraw care in much older patients as highlighted by Terman and colleagues (Terman et al., 2015). Overall, these findings contrast with those reported by Terman et al., who found that age was an independent predictor of poor neurological outcome despite adjusting for the

influence of chronic comorbidities by incorporating CCI and Charlson-age index into logistic regression analysis. Dementia was the only comorbidity found to be significantly associated with poor neurological outcomes in univariate analysis. Conversely, dementia was identified as a protective factor in survival to discharge in a study designed to develop a clinical prediction rule for survival from cardiac arrest in hospitalised patients in a North American centre, although outcome measures in this retrospective observational study did not incorporate further assessment of neurological function beyond hospital discharge (Merja, Lilien, & Ryder, 2015). The authors note the challenges associated with diagnosis and prognostication in dementia, suggesting that hospitalised dementia patients who undergo resuscitation may be more likely to be those with less advanced disease due to increasing use of advance directives where resuscitation would likely prove futile.

Clearly there are appreciable differences in study samples, notably that Terman et al. included all non-traumatic cardiac arrest patients aged eighteen and over, whereas Libungan et al. only included patients aged 70 and above. The former represents an ED population in a single North American centre, whereas the latter incorporates national Swedish cardiac arrest registry analysis. Previous attempts to define predictors of survival in older out-of-hospital cardiac arrest patients have proved problematic, not least because of the complexities involved in accounting for comorbidities and the distinction between chronological and physiological age (van de Glind et al., 2013). The CCI was neither designed nor validated for use in cardiac arrest populations. Furthermore, the validity of the scoring system has been questioned in the context of contemporary healthcare, given the significant advances made in treatment and management of chronic conditions and a general trend towards increased life expectancy (Quan et al., 2011). Although both studies report the apparent influence of increasing age on mortality following out-of-hospital cardiac arrest, the limitations associated with observational methodology are acknowledged, and the authors conclude that age alone remains an imperfect predictor of outcome and should not be used in isolation to guide resuscitation decisions (Libungan et al., 2015; Terman et al., 2015).

Prior to publication of the studies discussed above, a systematic review was conducted in an attempt to clarify pre-arrest predictors of survival in older patients after resuscitation from non-traumatic out-of-hospital cardiac arrest (van de Glind et al., 2013). The reviewers defined elderly patients as those aged above 70 years, and included studies where the mean age of participants was 70 years or above, or the study reported different age groups separately and included patients aged above 70 years. Studies solely reporting rates of ROSC or hospital admission rather than survival to discharge or neurological outcome were excluded. A total of 22 studies were included following a literature search incorporating publications from 1980-2011. The majority of studies were conducted in the

USA (n=13) or Europe (n=8). The remaining paper was a single nationwide population study from Korea (Ahn et al., 2010). Chart review or retrospective cohort methodologies accounted for the majority, with the exception of a single case-control study. A total of four exclusively recruited older patients, of which three were conducted in nursing home or long term care facilities (Applebaum, King, & Finucane, 1990; Awoke, Mouton, & Parrott, 1992; Ghusn, Teasdale, Pepe, & Ginger, 1995). The majority of studies overall scored a low-to-moderate risk of bias in relation to study participation, attrition and measurement of prognostic factors. In a number of cases the rationale for not reporting on an entire cohort or for exclusion of specific sub-groups was unclear. Measures of comorbidity or functional dependence were infrequently reported.

Fourteen studies were considered sufficiently clinically homogenous to perform meta-analysis for the primary survival outcome measure. For patients aged 70 years and above, pooled overall survival to discharge was 4.1% (95% CI 3.0-5.6%). The authors note that this was lower than that reported from a previous meta-analysis of survival in a more general resuscitation population (7.6%, 95% CI 6.7-8.4%) (Sasson et al., 2010). Further outcome analysis incorporating meta-analysis of odds ratios was discounted due to wide variety in the statistical methods employed and adjustment for confounding. Individually, all studies were noted to report a general trend towards decreased survival in the presence of increasing age in both univariate and multivariate analyses. Only one study investigated the predictive value of pre-arrest comorbidities, however this was in the context of an evaluation of the expansion of an automated defibrillator programme in a general resuscitation population in a single region of Italy and therefore not solely confined to older patients (Fabbri et al., 2006). Pre-existing hypertension, diabetes, myocardial infarction or congestive heart failure were associated with worsened outcomes. This contrasts with later work where dementia was the only comorbidity identified in univariate analysis to be negatively associated with survival (Terman et al., 2015).

The broad time period included in the search strategy resulted in retrieval and selection of studies spanning several decades, during which time there have been a number of relevant changes and developments in clinical practice. These include increasing use of do not attempt resuscitation orders (Cherniack, 2002) and several changes to international resuscitation guidelines (Kudenchuk et al., 2012), both of which have the potential to bias outcome and study population demographics. Libungan et al. (2015) noted temporal trends towards increased survival following out-of-hospital cardiac arrest in a Swedish population from 1992-2013, which was mirrored in older patients (≥70 years). In addition, there was an increase in the incidence of resuscitation attempts over time in older patients, which was most pronounced in those aged >80 years. Studies that specifically

addressed those resident in nursing home or long-term care facilities (Applebaum et al., 1990; Awoke et al., 1992; Ghusn et al., 1995) are unlikely to be generalisable to the wider population and have the potential to bias outcome measures due to the likely comorbidities and prognoses present within such populations. Two such studies (Applebaum et al., 1990; Awoke et al., 1992) were included in the pooled survival to discharge estimates, despite the authors noting that a number of other studies identified nursing home residency as a factor independently associated with decreased chances of survival (Ghusn et al., 1995; Kim, Becker, & Eisenberg, 2000; Deasy et al., 2011). In keeping with more recent studies, van de Glind and colleagues conclude that although older patients have a lower chance of survival following out-of-hospital cardiac arrest, older age alone remains an unreliable criterion for predicting outcome or withholding resuscitation.

4.5.1 Summary

Age is an important factor influencing mortality and morbidity following cardiac arrest. However, it remains an imperfect predictor in isolation, as a small but appreciable number of older patients consistently survive an episode of out-of-hospital cardiac arrest with good neurological and functional outcomes. There is a key distinction between chronological and biological or physiological age, and a number of studies have sought to account for the impact of comorbidities and frailty in older populations through the use of various functional scales and measures. Trends in clinical decision making also appear to be important but difficult to quantify, with some studies highlighting a higher incidence of withdrawal of care in older patients. It is therefore important to ensure that the design of the study dataset incorporates fields relating to comorbidities and clinical management during the in-hospital course.

4.6 Presenting rhythm and survival

Two retrospective registry analyses investigated the influence of presenting cardiac arrest ECG rhythm on outcomes in adults (>18 years) suffering non-traumatic out-of-hospital cardiac arrest (Dumas & Rea, 2012; Mader et al., 2012). Mader and colleagues conducted a retrospective review from 2005-2010 of the Cardiac Arrest Registry to Enhance Survival (CARES) database to which EMS systems throughout the USA contribute cardiac arrest data according to Utstein reporting principles (Mader et al., 2012). Primary outcome measures were based on proportions surviving to discharge with a secondary outcome measure of favourable CPC score. Dumas and Rea (2012) reviewed similar data from a single registry populated by King County and Seattle EMS systems, including cases from 2001-2009. Survival to discharge was the sole outcome measure.

Review of the CARES registry yielded a final sample of 30,939 cases which were stratified according to whether the presenting arrest rhythm was initially shockable, converted to a shockable rhythm

during resuscitation, or was not shockable at any stage. Converted shockable and never shockable categories were further sub-divided according to whether the rhythm was PEA or asystole. Differences between the three groups were compared using one-way ANOVA or Chi Square test with multivariate analysis undertaken via logistic regression. Unadjusted survival rates were similar for converted shockable and never shockable patients (4.7% versus 4.1%, p=.008), but significantly lower than initially shockable patients (26.9%, p<.001). Adjusted odds of survival to discharge were similar between converted shockable (Adjusted OR 0.17, 95% CI 0.14-0.20) and never shockable (Adjusted OR 0.17, 95% CI 0.15-0.18) versus shockable patients. Proportions of patients with favourable neurological outcome were significantly higher in the initially shockable group (16.8%) when compared with the converted shockable (1.8%) and never shockable (1.6%) groups (p<.001).

Analysis of registry data by Dumas and colleagues employed conventional stratification of cardiac arrest rhythms into VF and pulseless VT, PEA and asystole, with no consideration of patients who developed a shockable rhythm during resuscitation attempts. Arrest aetiology was also considered and categorised as cardiac or non-cardiac. Of a total of 5,958 potentially eligible cases, 1,001 (17%) were discharged alive from hospital and were therefore included in the final analysis. Patient demographics and clinical characteristics were compared using Chi-square test for categorical variables and Wilcoxon test for continuous variables. Kaplan Meier survival curves were used to estimate survival rates at one, five and ten years. The most common non-cardiac aetiologies reported were respiratory (n=86, 41%) and drug overdose (n=46, 22%). Survival to discharge rates increased significantly for non-cardiac aetiologies and non-shockable rhythms over time (p=.02). Kaplan Meier curve survival estimates were 82% (80-84%) at 1 year, 78% (75-80%) at 2 years, 73% (70-76%) at 3 years and 64% (61-67%) at five years. Survival rates were lower for non-cardiac versus cardiac aetiologies and non-shockable versus shockable arrest rhythms (p<.001).

Results from both studies demonstrate that the presence of a shockable rhythm following out-of-hospital cardiac arrest is associated with improved odds of survival to hospital discharge and favourable neurological outcome. These results are consistent with findings from other studies investigating the influence of multiple factors on survival, which frequently identify that the presence of a shockable rhythm is associated with improved outcomes (Sasson et al., 2010). Dumas and colleagues identified that Utstein predictors of survival such as witnessed arrest and bystander CPR were less prevalent in out-of-hospital arrests of presumed non-cardiac origin, suggesting that these patients may have had a lower chance of survival from the outset. Equally, both studies demonstrated that although the proportions of patients presenting in non-shockable rhythms surviving to hospital discharge was lower, an appreciable number of these patients survived

neurologically intact. The subset of patients identified in the CARES registry analysis as having converted to a shockable rhythm during resuscitation attempts are of particular interest. Limited evidence exists regarding this phenomenon, and although survival was not significantly different between the never shockable and converted shockable groups, the authors suggest that the development of specific guidelines for such patients may be of value in improving future outcomes. Although both studies accessed well established robust data registries, results are subject to the limitations associated with retrospective review, including variable quality of clinical notes, challenges in extracting relevant data, and difficulties in establishing cause and effect (Gearing, Mian, Barber, & Ickowicz, 2006). The CARES registry comprises data from a range of EMS systems within North America which employ a variety of response models and practitioners with varying skill sets (Pozner et al., 2004), thus increasing the potential for bias and confounding (Peat, 2002).

4.6.1 Summary

The presence of a shockable rhythm is established as a longstanding predictor of improved survival following out-of-hospital cardiac arrest. It is a fundamental part of routine reporting as per Utstein guidelines and the host EMS service routinely collects data relating to the presenting ECG rhythm on the arrival of the first ambulance resource. The emergence of a new sub-group of converted shockable patients within the resuscitation literature is of significance, particularly as there are no standardised definitions for this and it is rarely reported. Delivery of shocks in a patient initially presenting in PEA or asystole is commonly used as a surrogate marker for conversion to a shockable rhythm, however this relies on accurate prehospital ECG diagnosis and appropriate management. Although current reporting mechanisms within the host EMS system will permit identification of converted shockable patients on the basis of this definition, the limitations associated with this approach must be acknowledged.

4.7 Gender

Established epidemiological trends indicate that the prevalence of coronary heart disease and associated mortality is higher in men in each decade of life until after 75 years of age (Mosca, Barrett-Connor, & Wenger, 2011). In previous research, this has in part been attributed to gender differences in clinical presentation resulting in differences and potential delays in clinical management (Berger et al., 2009). Other studies have attributed improved survival amongst female patients to the cardioprotective role of oestrogen (Kitamura et al., 2010). In keeping with this, a retrospective review of the Victorian Ambulance Cardiac Arrest Registry (VACAR) sought to investigate gender differences in outcomes from out-of-hospital cardiac arrest, including outcomes favouring younger women (Bray, Stub, Bernard, & Smith, 2013). Adult cases of cardiac arrest of

presumed cardiac aetiology occurring during 2003-2010 were identified from the VACAR database and analyses incorporating Student *t*-test, Mann Whitney U test, Chi-square and logistic regression conducted to explore outcome differences between men and women. A total of 24,469 patients fulfilling the study criteria were identified, with a median age of 73 years, of whom 36% were female. Males were more likely to exhibit factors associated with improved survival, including younger age (median 71 versus 78 years, p<.001), witnessed arrest (35% versus 27%, p<.001), bystander CPR (29% versus 22%, p<.001) and an initially shockable rhythm (22% versus 9%, p<.001). Logistic regression adjusting for outcome predictors known to affect survival demonstrated that women were more likely to survive to hospital admission (OR 3.47, 95% CI 2.19-5.50) but had equivalent survival to discharge to men (OR 1.11, 95% CI 0.92-1.33). Further adjusted analyses stratified according to decade of life found that younger men were more likely than older men to survive to discharge (OR 1.87, 95% CI 1.42-2.47, p<.001) and similarly younger women were more likely than older women to survive to discharge (OR 2.59, 95% CI 1.64-4.11, p<.001).

The authors conclude that their results do not support the theory that the cardioprotective effects of oestrogen in women of child bearing age may result in improved outcomes following cardiac arrest. Although Australian women were found to have a lower prevalence of factors associated with improved cardiac arrest survival, they were significantly more likely than men to survive to hospital admission. There were no significant gender differences in either overall survival to discharge and survival to discharge stratified according to decade of life. However, it should be noted that the small sample size in the sub-set of women aged <40 years meant that no exploration of gender differences stratified according to presenting rhythm was possible. This is a major limiting factor given the established associated between presenting rhythm and outcomes following out-of-hospital cardiac arrest (Terman, Hume, Meurer, & Silbergleit, 2014). The definition of cardiac aetiology was based on that reported by paramedics in the prehospital phase where limited diagnostic information, and therefore certainty, may be present. In addition, the sub-set of women aged 18-44 was used as a proxy for oestrogen status, but the actual oestrogen status of female patents was unknown.

A small number of additional studies have evaluated the influence of gender more generally on outcomes following out-of-hospital cardiac arrest. One study examined the relationship between gender and outcomes using data drawn from the North American Resuscitation Outcomes Consortium (ROC) registry for non-traumatic cardiac arrests occurring during 2005-2007 (Morrison et al., 2016). In a similar analysis, researchers examined the association of gender with outcomes using data from the International Cardiac Arrest Registry (INTCAR) for cases treated with MTH

following admission to one of 45 cardiac arrest centres based in Europe and the USA during 2006-2012 (Karlsson et al., 2015). In contrast to the ROC registry, which comprises a significant volume of EMS data, INTCAR is predominantly based on intensive care unit data.

Data from the ROC database provided 14,690 patients, of whom 5,340 (36.4%) were women with a mean age of 68.3 years and 9,350 (63.6%) were men with a mean age of 63.2 years. Chi square testing was performed to examine differences in outcomes according to gender or age, with multivariate regression analysis employed to assess the association between gender and outcome according to age as both a continuous variable and stratified according to decade of life. Of note, the unadjusted incidence rate for cardiac arrest between different sites ranged from 34-104 per 100,000 person years for women and from 64-123 person years for men. Potential explanations for this include variation in morbidity between different populations or differing approaches to initiation of CPR and subsequent management of cardiac arrest attempts between individual EMS agencies. Women were found to be less likely to suffer a witnessed cardiac arrest, receive bystander CPR or present in a shockable rhythm ($p<.001$). Adjusted odds of survival did not differ significantly between women versus men (OR 1.16, 95% CI 0.98-1.36), however women were more likely to achieve prehospital ROSC (OR 1.31, 95% CI 1.19-1.43). After adjustment for common Utstein survival predictors, women aged 15-45 were more likely to survive to discharge than men (OR 1.66, 95% CI 1.04-2.64), however this relationship was not mirrored in the cohort aged >55 years (OR 0.94, 95% CI 0.78-1.15). This conflicts with earlier findings using data from the Australian VACAR database, which found no significant variation in outcomes in younger women, although this study exclusively recruited patients with cardiac arrest of presumed cardiac aetiology (Bray et al., 2013).

Analysis of INTCAR data relating to 472 (28%) women and 1,195 (72%) men identified that men were more likely to receive bystander CPR (64% versus 58%, $p=.03$), present in a shockable rhythm (69% versus 52%, $p<.001$), and to have a presumed cardiac cause of arrest (86% versus 71%, $p <.001$). There was no significant difference in the proportions of witnessed arrests between men and women. Multivariate analysis adjusting for selected baseline characteristics demonstrated that male gender was significantly associated with survival to hospital discharge (OR 1.34, 95% CI 1.01-1.78) but not with good neurological outcome (OR 1.24, 95% CI 0.92-1.67). These results contrast with those identified from the ROC registry, however no further analysis stratified by age group was undertaken which may account for the disparity in findings. Equally it may reflect variation in demographics between the populations from which individual registry data are derived.

4.7.1 Summary

Whilst it is established that there is an association between gender and outcome in some studies, causative factors are poorly understood and there is frequently the potential for significant confounding due to the influence of age on morbidity. Although established epidemiological data confirm higher prevalence of cardiovascular disease in men until older age, this does not universally translate into improved outcomes for female patients in all studies. Adequate consideration will therefore need to be given to age as a confounding factor in gender-based assessment of outcomes, particularly in the context of multivariate analysis.

4.8 Adrenaline in out-of-hospital cardiac arrest

The administration of adrenaline has been regarded as one of the cornerstones of advanced life support management of out-of-hospital cardiac arrest for decades, although timing, doses and sequencing have periodically undergone modification with guideline changes (Kudenchuk et al., 2012; McQueen, Gates, & Perkins, 2012). Earlier studies assessing the efficacy of adrenaline administration in out-of-hospital cardiac arrest focussed on crude survival rather than neurological status as an outcome measure. A prospective observational study of one-month survival among patients undergoing intubation or administration of adrenaline following out-of-hospital cardiac arrest in Sweden recruited 10,966 patients during 1990-1995, of whom 42.4% received adrenaline (Holmberg, Holmberg, & Herlitz, 2002). Cardiac arrest was witnessed by bystanders in 60.2% of cases and by EMS personnel in a further 9.9%. Overall, 43.3% of patients presented in a shockable rhythm. Survival to one month was highest in patients presenting in a shockable rhythm where the arrest was witnessed by EMS (31.9%), followed by those with bystander witnessed arrest and shockable rhythm (9.6%). Lower survival rates were observed in unwitnessed shockable (4.0%) and non-shockable (0.9%) arrests. Patients administered adrenaline were less likely to survive to one month compared to those who did not receive the drug (n=156, 3.4% versus n=388, 6.3%, p<.0001). Patients administered adrenaline were less likely to present in a shockable rhythm (51% versus 60.9%, p<.0001), but more likely to suffer a witnessed arrest (70% versus 64.4%) and receive bystander CPR (34.6% versus 30.5%, p<.0001). Mean response times were also shorter in patients who received adrenaline (16 versus 19.3 minutes, p<.0001). In logistic regression analysis adrenaline was associated with decreased odds of survival at one month (OR 0.43, 95% CI 0.27-0.66). The authors acknowledge the limitations associated with observational approaches, noting that the majority of survivors are drawn from sub-groups who present in a shockable rhythm, achieve ROSC following a small number of shocks, and therefore are not exposed to intra-arrest adrenaline administration. Thus, adrenaline becomes a surrogate marker for non-shockable cardiac arrests or

prolonged resuscitation attempts, both of which are independently associated with reduced odds of survival (Sasson et al., 2010).

Given the limitations associated with observational approaches and the use of survival as an outcome measure, subsequent studies have sought to quantify the effect of adrenaline on neurological outcomes following out-of-hospital cardiac arrest (McQueen et al., 2012; Perkins, Cottrell, & Gates, 2014). A randomised double-blind placebo-controlled trial conducted within Western Australia EMS (Jacobs, Finn, Jelinek, Oxer, & Thompson, 2011) is regarded as one of the first studies to employ randomisation in an attempt to provide more definitive evidence in relation to the use of adrenaline in out-of-hospital cardiac arrest (Perkins et al., 2014). During the study period from 2006-2009, paramedics utilised study packs containing 10 ml syringes with either 0.9% saline placebo or 10mg adrenaline as part of all advanced life support resuscitation attempts in adult patients (≥ 18 years). Prior to this, adrenaline was not used in resuscitation attempts within this service due to lack of evidence regarding efficacy. The primary study endpoint was survival to discharge with secondary outcomes of prehospital ROSC (> 30 seconds) and CPC at hospital discharge. A priori sample size calculations indicated that 2,213 patients per study arm were required on the basis of a survival to discharge rate of 5%. It was initially planned that a total sample size of 5,000 would be achieved with the participation of other Australian ambulance services, however these services were subsequently unable to participate and the trial effectively became a single centre study.

A total of 4,103 cardiac arrests were attended during the study period. Of these, 3,502 were excluded from the trial including 2,513 where resuscitation was not attempted. Although 601 patients were randomised, in 67 cases the randomisation number was not recorded and therefore no further analysis was possible. Final analysis was therefore based on 262 patients in the placebo arm and 272 who were administered adrenaline. Patient and clinical characteristics were evenly distributed between study arms. The odds of prehospital ROSC were significantly higher in patients administered adrenaline (23.5% versus 8.4%, OR 3.4, 95% CI 2.0-5.6). Patients from the adrenaline arm were also more likely to be admitted from the ED to hospital (25.4% versus 13.0%, OR 2.3, 95% CI 1.4-3.6). There was no significant difference between the adrenaline and placebo groups in the number of patients surviving to hospital discharge (4.0% versus 1.9%, OR 2.2, 95% CI 0.7-6.3). Good neurological outcomes (CPC 1&2) were achieved in most survivors (n=14, 87.5%), with poor neurological outcomes (n=2, 12.5%) confined solely to the adrenaline arm. Logistic regression analysis demonstrated little change in the odds of ROSC with adrenaline (OR 3.5, 95% CI 2.1-6.0) or survival to hospital discharge (OR 2.1, 95% CI 0.7-6.3). Although final numbers included in analyses

were underpowered to detect a significant effect, the authors conclude that administration of adrenaline significantly increases the proportion of patients who achieve ROSC but not the numbers surviving to hospital discharge with good neurological outcome. Further limitations associated with this study include voluntary participation of paramedics, resulting in only 40% of eligible staff enrolling patients. Despite similar characteristics between study arms, the potential for relatively low levels of staff participation to bias recruitment cannot be ignored. This study serves to highlight the appreciable practical and ethical challenges associated with prehospital research (Lyon, Egan, et al., 2010).

More recently, a series of systematic reviews and meta-analyses have sought to combine study results to provide further insight into the role of adrenaline in out-of-hospital cardiac arrest. Atiksawedparit et al. performed a meta-analysis to determine the effect of prehospital adrenaline on the short term outcomes of ROSC and survival to hospital admission and long term outcomes on survival to discharge and CPC score (Atiksawedparit et al., 2014). A total of 15 studies with publication dates ranging from 1994 – 2013 were incorporated in the final review, including both traumatic and non-traumatic arrest populations. The majority employed observational methodology (n=14) with only one RCT. Pooled treatment effects were variously derived from between four to eight studies with combined populations ranging from 2,381 to 421,459. The effect of adrenaline administration was assessed via risk ratios (RR) pooled across studies using a random-effect mode with sources of heterogeneity explored via meta-regression analysis. Six cohorts of adult patients were pooled to estimate the effects of adrenaline (n=16,321) versus no adrenaline (n=405,138) on prehospital ROSC, demonstrating that adrenaline administration was associated with higher odds of ROSC (RR 2.89, 95% CI 2.36-3.54). Sub-group analysis of studies including solely non-traumatic arrests (n=3) demonstrated that this relationship persisted (RR 2.18, 95% CI 1.0-2.49). The effect of adrenaline on overall ROSC derived from 2,381 patients from four studies was not significant (RR 0.93, 95% CI 0.5-1.74). Eight observational studies investigated the effect of adrenaline on survival to hospital admission. Substantial heterogeneity was identified ($Q=77.08$, $d.f=7$, $p<.001$, $I^2=90.9\%$) and the pooled RR was not significant (RR 1.05, 95% CI 0.80-1.38). Excluding a single study sample exclusively addressing PEA decreased heterogeneity ($Q=12.91$, $d.f=6$, $p=.045$) yielding a RR of 1.15 (95% CI 1.00-1.34). Survival to discharge was reported in seven studies and suggested that prehospital adrenaline was associated with lower proportions of survivors (RR 0.69, 95% CI 0.48-1.00). No studies reporting more sophisticated measures of neurological outcome were identified, therefore no pooled analysis of CPC scores was undertaken. The authors conclude that adrenaline administration in out-of-hospital cardiac arrest significantly improved prehospital but not overall ROSC, admission to hospital or survival to discharge.

A further meta-analysis identified RCT and quasi-RCT studies comparing standard dose adrenaline versus no adrenaline, high dose adrenaline (>1mg), vasopressin or adrenaline and vasopressin combination in out-of-hospital non-traumatic cardiac arrest (Lin et al., 2014). The primary outcome was survival to hospital discharge, with secondary outcomes defined as survival to hospital admission and good neurological outcome (CPC 1&2). A combined sample of 12,246 patients was obtained from 14 studies conducted during 1992-2012. The only study comparing adrenaline with placebo was the RCT conducted in Western Australia discussed above (Jacobs et al., 2011). Pooled results from trials comparing standard versus high dose adrenaline (n=6) demonstrated that standard dose treatment was associated with decreased odds of ROSC (RR 0.85, 95% CI 0.75-0.97, p=.02) and survival to admission (RR 0.87, 95% CI 0.76-1.00, p=.049), but no difference in survival to discharge (RR 1.04, 95% CI 0.76-1.42, P=.83) or good neurological outcome (RR 1.20, 95% CI 0.75-1.96, p=.46). There were no significant differences between patients treated with adrenaline versus combined adrenaline and vasopressin in terms of ROSC (RR 0.96, 95% CI 0.89-1.04, p=.31), survival to admission (RR 0.88, 95% CI 0.73-1.06, p=.17), survival to discharge (RR 1.0, 95% CI 0.69- 1.44, p=.99) and neurological outcome (RR 1.32, 95% CI 0.88-1.98, p=.18). One trial compared adrenaline to vasopressin, finding no difference in ROSC (RR 0.93, 95% CI 0.66-1.31), survival to discharge (RR 0.68, 95% CI 0.25-1.82, p=.44), or neurological outcome (RR 0.68, 95% CI 0.25-1.82, p=.44). In keeping with findings from a previous systematic review (Atiksawedparit et al., 2014), the authors conclude that vasopressors such as adrenaline and vasopressin potentially increase prehospital ROSC and survival to admission but that this does not translate into improved survival to discharge and neurological outcomes.

A more recent meta-analysis compared outcomes for patients who received adrenaline before versus after hospital arrival, examining prehospital ROSC, survival at one-month, survival to discharge and presence of good neurological outcome (Loomba, Nijhawan, Aggarwal, & Arora, 2015). A total of 14 studies were retrieved providing 655,853 patients for pooled analyses. Of these studies, a single RCT was identified (Jacobs et al., 2011) with the remainder employing observational approaches. Analysis of nine studies comprising 640,258 patients found that adrenaline was associated with higher odds of prehospital ROSC (OR 2.84, 95% CI 2.28-3.54), although significant heterogeneity was present (χ^2 102.2, p<.001, I^2 96%). Based on a pooled sample of 647,770 patients from 5 studies, there was no significant difference in survival at one month between the two groups (OR 1.03, 95% CI 0.70-1.34, p=.85). Similarly, analysis of results from eight studies totalling 6,527 patients demonstrated no significant difference in survival to discharge (OR 0.82, 95% CI 0.46-1.48, p=.52). Neurological outcome assessed via CPC in 641,723 patients from nine studies demonstrated increased odds of poor neurological outcome associated with adrenaline administration (OR 0.51,

95% CI 0.31-0.84, p=.008). In a summary of outcome frequency comparing adrenaline versus no adrenaline, pooled analysis demonstrated prehospital ROSC in 19.7% versus 5.5 %, survival at one-month in 5.4% versus 4.5%, survival to discharge in 5.0% versus 4.9% and good neurological outcome (CPC 1&2) in 1% versus 2% respectively. Extrapolating these frequencies to a hypothetical population of 2,000 patients assuming equal proportions of patients receiving adrenaline versus no adrenaline, it is projected that the adrenaline group would have an additional 142 patients with ROSC, with additional survivors at discharge (n=1) and at one-month (n=9) and three additional patients with poor neurological outcome. Despite considerable heterogeneity, pooled data indicate that although adrenaline may be associated with higher rates of prehospital ROSC, this is likely to be at the expense of additional survivors with poor neurological outcome.

The theoretical advantages of adrenaline in resuscitation are based on known pharmacological effects attributed to α2 receptor stimulation, resulting in vasoconstriction and increased aortic pressure which, in turn, leads to increased coronary and cerebral perfusion pressure (Perkins et al., 2014). Evidence from multiple trials suggests that adrenaline likely increases the incidence of prehospital ROSC and potentially admission to hospital, but this does not translate into more patients surviving to discharge with satisfactory neurological function (McQueen et al., 2012; Atiksawedparit et al., 2014; Lin et al., 2014; Loomba et al., 2015). Although the macrovascular effects of adrenaline are well established, more recent attention has focussed on the potential influence of microvascular effects on outcomes in cardiac arrest. Animal studies predominantly employing swine models have demonstrated reduced cerebrocortical microvascular blood flow associated with adrenaline coupled with increased ischaemia manifested by reduced tissue $p0_2$ and increased tissue pCO_2 (Fries, Weil, Chang, Castillo, & Tang, 2006; Ristagno et al., 2009). Administration of adrenaline in swine models incorporating active compression-decompression and impedance threshold devices similarly demonstrated increased coronary and cerebral perfusion pressure at the expense of reduced cerebral blood flow and $ETCO_2$ (Burnett, Segal, Salzman, McKnite, & Frascone, 2012). In the majority of these studies, cardiac arrest was induced through induction of VF, therefore these results may be less applicable to other presenting rhythms. In a trial addressing dynamic effects of adrenaline in out-of-hospital cardiac arrest with a first monitored rhythm of PEA, patients were randomised to receive standard ALS incorporating adrenaline (n=101) versus modified ALS with intravenous drug delivery (n=73) (Nordseth et al., 2012). In this sample, adrenaline markedly increased the rate of transition from PEA to a shockable rhythm and from PEA to ROSC. This may be of particular relevance in light of recent interest in outcomes for patients who convert from an initially non-shockable to shockable cardiac arrest rhythm (Mader et al., 2012). Although no assessment of longer term survival of neurological outcomes measures was

undertaken, this study highlights the need for further research regarding the efficacy of adrenaline incorporating a range of aetiologies and presenting rhythms.

4.8.1 Summary

Although an established part of out-of-hospital advanced life support resuscitation, the evidence for adrenaline remains largely based on theoretical benefits with no clear evidence of any association with improvements in long term survival or neurological outcome. Very significant ethical and logistical issues have been reported in relevant studies, including perceptions of healthcare practitioners in relation to the value of adrenaline in terms of clinical outcomes. The influence of standardised resuscitation guidelines on patterns of adrenaline use is also significant, given that administration is delayed until after the third shock in shockable rhythms but given as soon as possible in non-shockable scenarios. The use of adrenaline may therefore become a surrogate marker for non-shockable rhythms and resuscitation attempts of a longer duration, both of which are associated with increased odds of poor neurological outcome. This is an important consideration when conducting multivariate analysis.

4.9 Coronary Angiography and Primary Percutaneous Coronary Intervention (PPCI).

Following the emergence of evidence supporting early referral of patients with ROSC for coronary angiography with primary percutaneous intervention after out-of-hospital cardiac arrest (Dumas et al., 2010), a number of regionalised systems of care have been established to support the delivery of this approach both within the UK and internationally (Marcusohn et al., 2007; Sunde et al., 2007; Iqbal et al., 2015). A systematic review and meta-analysis of 32 studies spanning publication dates from 1995-2011 pooled data to compare outcomes for patients with ROSC who underwent immediate coronary angiography following out-of-hospital cardiac arrest (Larsen & Ravkilde, 2012). Of these studies, seven with predominantly prospective methodology were supportive of immediate angiography. The remaining studies consisted of broadly equal proportions of prospective and retrospective methodologies and were inconclusive. No evidence suggesting inferior outcomes associated with angiography was identified. Fifteen studies investigated angiography in post ROSC patients with STEMI or left bundle branch block. Survival rates ranged between 41%-92% and included predominantly male patients with witnessed out-of-hospital cardiac arrest presenting in a shockable rhythm. Many studies were conducted prior to widespread use of therapeutic hypothermia. Individual sample sizes were generally small, with the largest derived from a retrospective observational study of 186 patients where an acute coronary occlusion was identified in 74% of cases (Garot et al., 2007). Rates of survival to hospital discharge and at six months were 55% and 54% respectively, with good neurological outcome achieved in the majority of cases.

Similar trends towards improved long-term neurological outcomes were observed in a number of other studies (Bendz et al., 2004; Lettieri et al., 2009).

A further five studies investigated outcomes for angiography in less clearly defined cohorts selected on the basis of a clinical decision that non-cardiac aetiology was unlikely. Survival ranged from 31%-81%, with angiographic signs judged to be consistent with acute myocardial infarction observed in 36%-69% of cases. ST segment elevation or left bundle branch block was present in 31%-63%. In the largest dataset (n=435) derived from a prospective registry, percutaneous coronary intervention following angiography was an independent predictor of survival (adjusted OR 5.2, p=.04) (Dumas et al., 2016). Pooled survival rates were based on studies incorporating patients with ROSC following cardiac arrest of mixed aetiology with angiography performed in selected patients (n=10). The proportions of patients exposed to acute angiography varied considerably between studies (14%-83%), as did other clinical variables such as the presence of a shockable rhythm (39%-100%). Pooled unadjusted odds of survival significantly favoured exposure to acute angiography post ROSC (OR 2.78, 95% CI 1.89-4.10). This represents crude mortality as insufficient data were able to facilitate adjusted analysis to control for selection bias and therefore these findings should be interpreted with caution, especially given the considerable heterogeneity identified (I^2 = 74%, p<.001).

More recently, a retrospective review evaluated outcomes for cardiac arrest patients with ST elevation conveyed directly to a HAC within a UK urban EMS system during April 2011 – March 2012 (Fothergill et al., 2014). The study population consisted of adult (≥ 18 years) patients with evidence of ST elevation myocardial infarction post ROSC. A total of 206 patients were transferred to a HAC following autonomous paramedic interpretation of the 12 lead ECG. Of these, 66% (n=131) survived to hospital discharge. Longer term survival outcomes were available for 122 of these, of whom 98% survived to 30-days and 97% to one-year post discharge. When compared with non-survivors, survivors tended to be younger (mean 59 versus 68 years, p<.001) and to have shorter intervals from emergency call to HAC arrival (mean 56 versus 75 minutes, p<.001), although this may be a surrogate marker for shorter time to ROSC which is associated with improved outcomes (Komatsu et al., 2013; Goto et al., 2016). More survivors also suffered witnessed cardiac arrests in public places and presented in a shockable rhythm, which is consistent with other studies examining factors associated with improved outcome post out-of-hospital cardiac arrest (Sasson et al., 2010). Although directly applicable to the UK setting, the authors were only able to determine that participants were directly transferred to a HAC, not whether they underwent angiography or percutaneous coronary intervention. Crude survival rates are reported, however no further

assessment of neurological status was undertaken. Finally, the absence of a comparator group limits the extent to which these results can be directly attributed to treatment at a HAC.

A much larger comparative study of outcomes for patients undergoing treatment at a designated STEMI centre (n=5,202) versus other facilities (n=1,869) in a North American setting evaluated neurological recovery at discharge following out-of-hospital cardiac arrest throughout 2011 (Mumma, Diercks, Wilson, & Holmes, 2015). Data were obtained from a statewide discharge database, with good neurological outcome defined as discharge to home, residential care facility, prison or another hospital for non-acute care. Multiple logistic regression was used to adjust for patient and clinical demographics, with hierarchical modelling to account for correlations within individual centres. In order to examine the effects of patient volume on outcomes, STEMI centres were stratified into those treating <40 patients annually versus those treating ≥40 patients. A total of 333 hospitals were able to receive post ROSC patients, of which 16% (n=54) were STEMI centres receiving ≥40 cases and annually and 21% (n=71) were STEMI centres receiving <40 cases annually. Overall, 24% of patients (n=1,869) were judged to have good neurological outcomes as per study criteria. Treatment at both high volume (≥40 cases) and low volume (<40 cases) STEMI centres was associated with higher odds of good neurological outcome (OR 1.35, 95% CI 1.13-1.62 and OR 1.71, 95% CI 1.42-2.07 respectively). Increased odds of good neurological outcome with STEMI treatment were also apparent in multivariate analyses for both high (OR 1.32, 95% CI 1.06-1.64) and low (OR 1.63, 95% CI 1.35-1.97) volume centres (p<.001). The presence of a shockable rhythm was associated with increased odds of good outcome (OR 1.97, 95% CI 1.75-2.21, p<.001), whilst increasing decade of life was associated with lower odds of good outcome (OR 0.87, 95% CI 0.83-0.90, p<.001). Proportions of patients with good neurological outcome within individual STEMI centres ranged from 0%-68%. This relationship persisted following multivariate analysis controlling for variables such as age, gender and presenting arrest rhythm (p<.001), suggesting that variation in hospital practices between individual centres may play an important role in influencing outcomes. However, it is important to note that a number of variables such as witnessed arrest and bystander CPR were unknown and therefore could not be incorporated as part of multivariate analysis. Study criteria for determining good neurological outcome were broad which may have led to patients with relatively significant cognitive impairment being categorised as having good outcomes. The use of discharge destination as a surrogate marker of functional status is a relatively crude measure when compared with more sophisticated outcome scales such as CPC and mRS (Rittenberger et al., 2011).

4.9.1 Summary

A large volume of literature is supportive of the use of angiography and primary percutaneous coronary intervention in out-of-hospital cardiac arrest survivors. There is considerable variation between these studies in terms of the inclusion and exclusion criteria for direct transfer to a facility capable of delivering these interventions rendering comparison of results challenging. The most compelling evidence relates to patients with evidence of STEMI, and this is reflected in the criteria used by the host EMS system to identify patients for direct HAC transfer post ROSC. However, intervention in patients with other post ROSC ECG patterns is associated with promising outcomes although the proportions of those found to have acute coronary lesion is usually less in these groups. Patients exposed to percutaneous coronary intervention are also frequently provided with additional therapeutic interventions such as therapeutic hypothermia which may also introduce an element of confounding (Wolfrum, Pierau, Radke, Schunkert, & Kurowski, 2008). This therefore highlights the importance of collecting sufficient data to provide a clear picture of in-hospital management following HAC transfer.

4.10 Therapeutic hypothermia and targeted temperature management

In recent years, renewed interest in mild therapeutic hypothermia has led to concomitant cooling treatment being routinely offered to post ROSC out-of-hospital cardiac arrest patients undergoing angiography and PPCI (Casella et al., 2015). In 2002, the results of two landmark trials of mild therapeutic hypothermia (MTH) following out-of-hospital cardiac arrest in Europe (Hypothermia after Cardiac Arrest Study Group, 2002) during 1996-2001 and Australia (Bernard et al., 2002) during 1996-1999 were published. Both studies included adult (≥18 years) patients with out-of-hospital cardiac arrest presenting in a shockable rhythm and excluded patients with apparent non-cardiac aetiology. Pregnancy was an exclusion criterion in both studies, with Australian researchers excluding all women aged <50 years for this reason. Randomisation to normal treatment versus induction of MTH was undertaken on ED arrival in nine centres within Europe whereas paramedics in the Australian study randomised patients and commenced cooling through the application of cold packs to the head and torso in the prehospital phase. MTH was maintained or initiated in both hospital settings via the application of external cooling devices, with temperature monitoring via bladder temperature probes to achieve targets of 32-34^{o}C (Hypothermia after Cardiac Arrest Study Group, 2002) and 33^{o}C (Bernard et al., 2002) respectively. Sedation, paralysis and ventilation was provided to all MTH patients in both studies. Assessment of neurological outcome was via CPC in European patients and via discharge destination in Australian patients, with good outcomes defined as CPC 1&2 (Hypothermia after Cardiac Arrest Study Group, 2002) and discharge home or to rehabilitation facility (Bernard et al., 2002).

The Hypothermia After Cardiac Arrest Study Group recruited a total of 275 patients, of whom 137 were randomised to the MTH group, although hypothermia was discontinued early in 14 of these due to death (n=6), arrhythmia with haemodynamic instability (n=3), technical problems (n=2), liver rupture (n=1), randomisation difficulties (n=1) and error in duration of cooling (n=1). Corresponding figures in the Australian sample were 77 patients of whom 43 were randomised to MTH, with failed randomisation in four patients due to physician decision (n=3) and inadvertent rewarming (n=1). Both studies concluded that MTH improved neurological outcomes in patients following resuscitation from out-of-hospital cardiac arrest. In the European sample, 55% (n=75) of patients undergoing MTH achieved good neurological outcomes versus 39% (n=54) in the standard treatment arm (RR 1.40, 95% CI 1.08-1.81). Mortality at 6 months was lower in the MTH group (41% versus 55%, RR 0.74, 95% CI 0.58-0.95). The Australian study reported good outcomes in 49% (n=21) of patients randomised to MTH versus 26% (n=9) undergoing standard care (p=.046). Odds of good outcome adjusting for age and time to ROSC were higher in patients exposed to MTH (OR 5.25, 95% CI 1.47-18.76, p=.001). Neither study found any significant difference in the proportion of adverse events between trial arms, although a non-significant trend towards a higher incidence of sepsis in MTH patients was noted in the European sample.

These findings were initially regarded with caution by the international resuscitation community, with calls for further larger scale trials and improved understanding of the apparent neuroprotective mechanisms associated with MTH and optimal treatment regimens (Nolan, Morley, Hoek, & Hickey, 2003). The narrow inclusion criteria applied in each study limits the generalisability of these findings to more general resuscitation populations. Significant differences in the timing and duration of initiation of MTH are also apparent, with patients in the Australian trial undergoing cooling earlier during the prehospital phase but exposed to a shorter period of MTH overall when compared with the European trial (Lyon, Richardson, et al., 2010). These findings have more recently been called into question following a larger multi-centre trial randomising comatose (GCS <8) patients (n=939) admitted to Intensive Care Units within Europe and Australia following resuscitation from out-of-hospital cardiac arrest with presumed cardiac aetiology to targeted temperature management at either 33^{o}C or 36^{o}C (Nielsen et al., 2013). Patients were enrolled regardless of presenting rhythm, although cases presenting in asystole following unwitnessed arrest and those with suspected intracranial bleed or temperature <30^{o}C were excluded. A priori sample size calculations indicated that a sample size of 900 would be required to provide 90% power to detect a 20% reduction in the hazard ratio (HR) for death between the trial arms at a two-sided alpha level of 0.05.

The primary outcome measure was all-cause mortality, with a composite secondary outcome of poor neurological function (CPC 3-5 or mRS 4-6) or death at 180 days. There was no significant difference in mortality between the 33^{o}C and 36^{o}C arms at trial end (50%, n=235 versus 48%, n=225, HR 1.06, 95% CI 0.89-1.28, p=.51). Similarly, there were no significant differences in the proportions of patients who had poor neurological outcome assessed via CPC (54%, n=251 versus 52%, n=242, HR 1.02, 95% CI 0.88-1.16, p=.78) or mRS (52%, n=245 versus 52%, n=239, HR 1.01, 95% CI 0.89-1.14, p=.87) or had died (48%, n=226 versus 47%, n=220, HR 1.01, 95% CI 0.87-1.15. p=.92) at 180 days. The authors conclude that induction of MTH at 33^{o}C versus targeted temperature management to maintain patients at 36^{o}C confers no additional benefit. This study has several advantages when compared with earlier trials relating to MTH (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002), not least that it is appropriately powered and incorporates a broader range of presenting rhythms thus enabling greater generalisability. One interpretation of these findings is that it is in fact prevention of fever rather than induction of MTH that confers survival and outcome benefits (Fukuda, 2016). Indeed mean body temperature approached 38^{o}C in patients randomised to standard care in the earlier European study (Hypothermia after Cardiac Arrest Study Group, 2002), suggesting that worsened outcomes in this group may have been due to absence of fever control rather than non-exposure to MTH (Fukuda, 2016).

Several studies have investigated immediate cooling following out-of-hospital cardiac arrest, however a recent meta-analysis concluded that there were no significant outcome benefits derived from initiation of MTH in the prehospital phase (Hunter, O'Donnell, Allgood, & Seupaul, 2014). A UK based observational study prospectively monitored oesophageal temperature in the prehospital phase in patients who achieved ROSC following out-of-hospital cardiac arrest and in all cases brought to a single ED who achieved ROSC and were admitted to ICU (Lyon, Richardson, et al., 2010). All adult non-traumatic cases of unwitnessed cardiac arrest who remained comatose were eligible for inclusion. Temperature was monitored until a target of 34^{o}C was achieved. A total of 164 patients were included in the study, of whom 64% (n=105) died in the ED. The remainder (n=59) were admitted to ICU for cooling, with 11.6% (n=19) surviving to discharge. Patients in whom temperature was measured in the prehospital phase were universally hypothermic (mean 33.9^{o}C, 95% CI 33.2-34.5^{o}C) as were those in whom temperature was measured on ED arrival (mean 34.3^{o}C, 95% CI 34.1-34.6^{o}C). Patients surviving to discharge were warmer on admission to ICU than those who died in hospital (35.7^{o}C versus 34.3^{o}C, p<.05). Despite the limitations associated with a relatively small sample size and observational methodology, this study suggests that patients with prehospital ROSC in the UK setting are likely to be initially hypothermic regardless of any temperature management interventions.

4.10.1 Summary

Recent evidence has challenged assumptions regarding the role and therapeutic value of mild hypothermia in the post ROSC phase, although it remains clear that fever is associated with worsened outcomes. Recording temperature in the prehospital post-ROSC phase is therefore an important physiological measure both in terms of predicting outcome and determining the potential need for out-of-hospital temperature control strategies. Temperature is measured within the host EMS system via tympanic thermometer. This contrasts with some of the more invasive methods discussed in the studies above, however it does provide a consistent means of recording temperature which will be of value in determining the prevalence of fever within the study population and investigating the potential prognostic value of this measure.

4.11 Cardiogenic shock

Cardiogenic shock remains the leading cause of death for hospitalised patients following acute myocardial infarction (Hochman et al., 1999). The presence of shock in the post ROSC phase is therefore a potential predictor of outcome and an important area for targeted therapeutic intervention (Stegman, Newby, Hochman, & Ohman, 2012). A review of data collected prospectively during 2003-2011 within an Australian EMS system examined the influence of last recorded prehospital systolic blood pressure (SBP) on outcomes for adult patients (≥18 years) with ROSC sustained to hospital following out-of-hospital cardiac arrest of presumed cardiac aetiology (Bray, Bernard, Cantwell, Stephenson, & Smith, 2014). The primary outcome measure was survival to discharge, with all cases where the arrest was witnessed by EMS or hospital staff excluded from analysis. A total of 3,620 cases were identified with a mean age of 69 years (IQR 58-78), of whom 70% (n=2,550) were male and 60% (n=2,180) presented in a shockable rhythm. Last recorded prehospital blood pressures were stratified into unrecordable, <80 mmHg and 10 mmHg increments thereafter. Median blood pressure was higher in patients presenting in shockable versus non-shockable rhythms (123 mmHg versus 120 mmHg, p<.001), although this is unlikely to be clinically significant. Patients presenting in non-shockable rhythms were more likely to be hypotensive (SBP <90mmHg) than those found in a shockable rhythm (19% versus 10%, p<.001). Overall rates of hypotension declined over time from 22% in 2003 to 8% in 2011 (p<.001). Multivariate analysis adjusting for confounders known to influence survival demonstrated that in shockable rhythms lower odds of survival were observed in patients with SBP 80-89 mmHg (OR 0.49, 95% CI 0.24-0.95), SBP <80 mmHg (OR 0.24, 95% CI 0.10-0.61) and unrecordable SBP (OR 0.10, 95% CI 0.04-0.30). There was no significant relationship between SBP and survival in non-shockable cases (OR 1.01, 95% CI 0.89-1.15). These results should be interpreted in the context of an EMS system with more aggressive approaches to inotropic support and fluid therapy post ROSC than those within UK

services (Deakin et al., 2015). Furthermore, the authors could not determine the prehospital management provided to each patient, therefore it is unclear whether arrival SBP reflects more serious illness or sub-optimal management by EMS.

Ostenfeld and colleagues retrospectively compared outcomes between patients with a diagnosis of acute myocardial infarction complicated by cardiogenic shock with and without cardiac arrest prior to admission to a single HAC (Ostenfeld et al., 2015). Cardiogenic shock was defined as per parameters used in the SHOCK trial, incorporating systolic BP <90 mmHg, signs of organ hypoperfusion, and ongoing requirement for fluids and inotropes (Hochman et al., 1999). A total of 517 patients fulfilling these criteria with spontaneous circulation were admitted between 2008-2013, of whom 269 were excluded due to non-ischaemic causes of shock such as hypovolaemia. In the remaining patients (n=248), 48% (n=118) had achieved ROSC post out-of-hospital cardiac arrest. Of the cardiac arrest cases, a shockable rhythm was present in 64% (n=76), the arrest witnessed in 71% (n=84) and bystander CPR performed in 69% (n=58). Patients in the cardiac arrest group were younger than those in the non-arrest group (median 64 versus 68 years, p=.03). Survival rates were calculated via Kaplan-Meier plots with proportional hazard models and multivariate analysis employed to adjust for confounders known to influence survival. Outcome comparisons between the arrest and non-arrest groups demonstrated no significant differences in one-week mortality (63% versus 56%) or long term mortality (76% versus 77%). In multivariate analysis, the presence of out-of-hospital cardiac arrest was not found to be an independent predictor of long-term mortality (HR 1.08, 95% CI 0.82-1.44), however older age was associated with a lower likelihood of longer term survival (HR 1.02, 95% CI 1.01-1.03). Systolic blood pressure at hospital admission did not differ significantly between the arrest versus non-arrest cohorts (mean 84 mmHg versus 85mmHg), although the precise times at which physiological signs were recorded and details of any prehospital interventions are unclear. Although details of prehospital interventions were equally unclear in the Australian EMS study, last recorded prehospital systolic blood pressure was used as the marker of haemodynamic status (Bray et al., 2014), thus avoiding confounding relating to the influence of immediate hospital-based interventions. Despite previous evidence of higher mortality associated with myocardial infraction when complicated by cardiac arrest (Lettieri et al., 2009; Dumas et al., 2010), the authors assert that out-of-hospital cardiac arrest is not independently associated with worsened outcomes in patients presenting in cardiogenic shock and therefore aggressive revascularisation strategies remain appropriate in this patient group.

4.11.1 Summary

The presence of cardiogenic shock remains an important predictor of outcome, although some evidence suggests that this may be more pronounced in non-shockable versus shockable cohorts of cardiac arrest patients. Reliable identification of the presence of cardiogenic shock during the prehospital ROSC phase may be challenging due to inconsistencies in the availability of continuous monitoring data for blood pressure and other markers of haemodynamic instability. This may result in failure to identify transient periods of cardiogenic shock and difficulties in assessing haemodynamic changes resulting from prehospital intervention such as the administration of inotropic support. Equally, identification of a single hypotensive blood pressure measurement may result in inappropriate diagnosis of cardiogenic shock. In several settings, including the host EMS system, prehospital practitioners are permitted to provide intravenous fluids and inotropic support including the use of adrenaline in patients fulfilling local criteria for haemodynamic instability. Given the potential adverse events and negative outcomes associated with adrenaline in some studies, it may be difficult to determine whether outcomes in the planned study are the result of cardiogenic shock per se or potentially harmful interventions initiated in response to identification of haemodynamic instability. As discussed earlier, this will be an important consideration in planning multivariate analysis.

4.12 End Tidal CO_2

Levels of alveolar and therefore end tidal CO_2 are determined by CO_2 production, alveolar ventilation and pulmonary blood flow. In low flow states, $ETCO_2$ primarily reflects pulmonary blood flow. In the context of cardiac arrest, this is largely generated through chest compressions and therefore there is considerable interest in the prognostic value of $ETCO_2$ in relation to quality of CPR and survival outcomes (Levine, Wayne, & Miller, 1997). Early studies relating to $ETCO_2$ in cardiac arrest were predominantly conducted in hospital (Garnett, Ornato, Gonzalez, & Johnson, 1987; Falk, Rackow, & Weil, 1988; Sanders, Kern, Otto, Milander, & Ewy, 1989). However, the subsequent extension of $ETCO_2$ monitoring capabilities to ALS resources within North American EMS systems permitted further research in the out-of-hospital setting (Asplin & White, 1995; Levine et al., 1997). Two such studies employed prospective observational approaches to explore the prognostic value of $ETCO_2$ in cardiac arrest. The first enrolled 27 patients with non-traumatic arrests (Asplin & White, 1995) whilst the second recruited a larger sample (n=150) of patients presenting in or converting from asystole to PEA with no evidence of trauma, poisoning, tension pneumothorax, cardiac tamponade, hypovolaemia or hypothermia (Levine et al., 1997).

Asplin and White found that mean $ETCO_2$ was higher in patients who achieved ROSC versus those who did not when values were recorded at one (23 mmHg versus 13.2 mmHg, p=.002) and two minutes (26.8 mmHg versus 15.4 mmHg, p=.0019). Maximum $ETCO_2$ was also higher in the ROSC group (30.8 mmHg versus 22.7 mmHg, p=.0154). In contrast, Levine and colleagues found no difference in initial $ETCO_2$ (12.3 mmHg versus 12.2 mmHg, p=.93) but reported that $ETCO_2$ at 20 minutes was significantly higher in those who survived to admission versus those who died pre-admission (32.8 mmHg versus 4.4 mmHg, p<.001). An important distinction between these studies is that paramedics employed mechanical ventilation in the first (Asplin & White, 1995) and hand ventilation via self-inflating bag in the second (Levine et al., 1997), increasing the potential for hyper and hypoventilation to affect $ETCO_2$ readings (Pokorna et al., 2010). However, the variation in utility of $ETCO_2$ as a predictor of outcome is also likely a reflection of clinical demographics, particularly given the exclusion of shockable rhythms in the larger sample. This is supported by later research, which identified significant variation in $ETCO_2$ depending on the presenting rhythm, aetiology and the time interval during which $ETCO_2$ values were recorded (Lah, Krizmaric, & Grmec, 2011).

A series of observational studies conducted within physician based EMS systems in Slovenia (Grmec & Klemen, 2001; Kolar, Krizmaric, Klemen, & Grmec, 2008) and the Czech Republic (Pokorna et al., 2010) investigated the prognostic value of $ETCO_2$ in out-of-hospital cardiac arrest. The Slovenian studies prospectively recruited samples of 139 (Grmec & Klemen, 2001) and 737 (Kolar et al., 2008) adult (≥18 years) patients during 1999-2000 and 1998-2006 respectively. Higher rates of ROSC (59.4%, n=438 versus 38%, n=53) and survival to hospital discharge (23%, n=170 versus 17%, n=23) were observed in the later study. In the first study, the first, final, minimum, maximum, and mean values for $ETCO_2$ were recorded and incorporated into sensitivity analysis, whereas in the later study $ETCO_2$ was recorded as a continuous variable permitting multivariate analysis and calculation of ROC curves. Higher mean initial $ETCO_2$ levels were observed in survivors versus non-survivors by both Grmec and Klemen (2001) (19.7 mmHg +/- 4.8 versus 9.9 mmHg +/- 6.3, p<.01) and Kolar et al. (2008) (23.8 mmHg +/- 10.7 versus 17.6 mmHg +/- 14.7, p<.001). Kolar et al. also found significantly higher initial $ETCO_2$ values in patients presenting in PEA versus shockable rhythms (25.6 mmHg +/- 18.1 versus 16.6 mmHg +/- 9.8). Conversely, once resuscitation was commenced lower $ETCO_2$ values were then observed in cases of PEA at both one minute (24.8 mmHg +/- 10.5 versus 21.1 mmHg +/- 11.3, p<.001) and as an average of the first 10 minutes of resuscitation (17.3 mmHg +/- 8.3 versus 13.5 mmHg +/- 0.9, p<.001). Using a cut off value of 10mmHg for initial, average and final $ETCO_2$ values correctly identified 100% of the patients subsequently resuscitated in the smaller sample with corresponding specificities of 74.1%, 90.0% and 81.4% respectively (Grmec & Klemen, 2001). Similarly, Kolar and colleagues reported that no patient with $ETCO_2$ < 10 mmHg achieved ROSC,

concluding that $ETCO_2$ values of >14.3 mmHg measured after 20 minutes of resuscitation identified patients who would achieve ROSC with 100% sensitivity, specificity and positive and negative predictive values. Using a cut-off value of 13.5 mmHg in patients presenting in a shockable rhythm and 15.8 mmHg in those with non-shockable rhythms achieved 100% sensitivity and negative predictive value for discharge from hospital.

Building on these results, researchers from the Czech Republic sought to analyse changes in $ETCO_2$ during the peri-ROSC phase of resuscitation to determine whether increases in $ETCO_2$ values could be used as a reliable indicator of ROSC (Pokorna et al., 2010). A total of 140 patients were initially identified, of whom 32 were excluded due to unstable non-sustained ROSC. The remaining cases were dichotomised into those with a single episode of sustained ROSC (n=59) and those with no signs of ROSC at any stage (n=49). In addition to the $ETCO_2$ value at the point of ROSC, mean $ETCO_2$ values before and after ROSC and minimum and maximum values during the pre and post ROSC phases were recorded and analysed via the paired *t*-test. Mean duration of $ETCO_2$ recording in the ROSC cases (n=59) was 18 minutes pre ROSC and 33 minutes post ROSC. Averaged mean levels of $ETCO_2$ across these cases before ROSC were 26.65 mmHg +/- 12.44 and 36.60 mmHg +/-12.44 following ROSC ($p<.0001$). Paired *t*-test results comparing individual changes in $ETCO_2$ demonstrated a significant increase in values at the time of ROSC ($p<.0001$). The mean difference in $ETCO_2$ immediately before and after ROSC was 9.95 mmHg (95% CI 6.46-13.50). Mean duration of recordings from patients with no ROSC (n=49) was 29 minutes, with averaged mean $ETCO_2$ value of 16.68 mmHg +/-9.1. These results are consistent with previous findings that $ETCO_2$ values are higher in patients who subsequently achieved ROSC (Grmec & Klemen, 2001; Kolar et al., 2008). The authors conclude that as well as the utility of $ETCO_2$ values for prognostication, a sudden increase >10 mmHg may also be used to alert rescuers to the potential for ROSC and the need to perform further assessment for signs of circulation.

$ETCO_2$ is routinely measured within UK ambulance services in ventilated patients. Evidence suggests that $ETCO_2$ values have utility both in terms of prognostication and indicating the likely presence of ROSC. $ETCO_2$ also has an important role in confirmation of correct positioning of the endotracheal tube (Woollard & Furber, 2010) and providing a surrogate marker for quality of CPR (Sheak et al., 2015). Finally, it is established that hyperventilation occurs frequently and is harmful in cardiac arrest. Waveform capnography provides contemporaneous quantitative feedback and may facilitate more appropriate ventilatory strategies post ROSC (Bobrow & Ewy, 2009). Recording and interpretation of $ETCO_2$ results is therefore an important part of cardiac arrest management and research.

4.12.1 Summary

$ETCO_2$ monitoring has an important role in confirming correct positioning of an endotracheal tube, monitoring the on-going effectiveness of resuscitation efforts, identifying ROSC and predicting outcome. There is some evidence of variation in $ETCO_2$ associated with the presenting ECG rhythm, ventilation patterns, timing of measurement, and administration of adrenaline. In keeping with blood pressure, continuous values for $ETCO_2$ are not consistently available within the host EMS system, which raises important concerns regarding the reliability of single isolated $ETCO_2$ measurements for both research and prognostication purposes. Multiple factors may influence $ETCO_2$ values at any given stage in the prehospital resuscitation attempt and this will need careful consideration as part of pre-planned statistical analyses.

4.13 Glycaemic control

Capillary blood glucose monitoring is routinely available within UK ambulance services and is commonly measured as part of out-of-hospital cardiac arrest management (Soar et al., 2013). Current resuscitation guidelines acknowledge the potentially deleterious effects of derangements in blood glucose post ROSC, and recommend that glucose levels are maintained at ≤ 10 mmol/l, although strict glucose control is not recommended due to the equally damaging effects of hypoglycaemia (Nolan et al., 2015). Retrospective analyses of in-hospital registry data in the United States (Beiser, Carr, Edelson, Peberdy, & Hoek, 2009) and the UK (Nolan et al., 2007) have identified that both hyper and hypoglycaemia are associated with worsened outcomes following cardiac arrest. Although examining outcomes after in-hospital cardiac arrest, Beiser and colleagues reported decreased adjusted survival odds within a sample of 3,218 patients for non-diabetics exhibiting blood glucose levels outside the range 6.2-13.3 mmol/l. Higher proportions of non-diabetic patients survived to discharge when compared with those with a history of diabetes (45.5%, 95% CI 43.3-47.6% versus 41.7%, 95% CI 38.9-44.5%, p=.37). A similar U-shaped relationship was identified from UK data based on minimum blood glucose levels recorded in the first 24-hours after admission to ICU in 28,958 post ROSC patients, 13.8% (n=8,987) of whom had suffered out-of-hospital cardiac arrest. Adjusted odds of hospital mortality were 1.21-1.31 for each 1 mmol/l decrease below 5 mmol/l and 1.05-1.08 for every 1 mmol/l increase above 7 mmol/l.

Retrospective analysis of prehospital cardiac arrest registry data in Helsinki found similar relationships between blood glucose derangement and worsened clinical outcomes in a sample of 134 adult (≥18 years) patients presenting in a shockable rhythm following witnessed out-of-hospital cardiac arrest during 2005-2009 (Nurmi, Boyd, Anttalainen, Westerbacka, & Kuisma, 2012). Prehospital blood glucose levels were obtained via capillary (n=106), arterial (n=24) and venous

(n=4) samples and there was no significant difference in time to sampling between survivors and non-survivors (105 minutes IQR 85-132 versus 114 minutes IQR 91-129, p=.3157). Overall, 65% (n=87) of patients survived with good neurological outcome (CPC 1&2). There was no significant variation in prehospital and admission values in surviving patients (10.5 mmol/l +/- 4.1 versus 10.0 mmol/l +/- 3.7, p=.3483), whereas a significant increase was observed in non-survivors (13.8 mmol/l +/- 3.3 versus 11.8 mmol/l +/- 4.6, p=.0025). Non-survivors continued to exhibit higher blood glucose concentrations than survivors at 0-3 hours (13.5 mmol/l +/- 3.9 versus 10.4 mmol/l +/- 4.3, p<0.0001), 3-6 hours (10.2 mmol/l +/-4.4 versus 8.2 mmol/l +/- 2.7 p<.001) and 6-12 hours (7.5 mmol/l +/- 2.2 versus 6.6 mmol/l +/-1.6, p<.001) following admission.

Similar analysis of prehospital data from an Australian ambulance cardiac arrest registry included all adult (>15 years) patients regardless of presenting rhythm who suffered cardiac arrest of presumed cardiac aetiology during 2007-2015 (Nehme, Nair, et al., 2016). Primary outcome measures were survival to discharge and functional status at 12-months measured via the Extended Glasgow Outcome Scale (eGOS). A total of 11,873 patients met the inclusion criteria, of whom 20.5% (n=2,438) had a previous history of diabetes documented. Blood glucose levels are recorded infrequently and exclusively via capillary samples in this EMS system, therefore these data were only available in 11.1% (n=1,319) of eligible cases. Survival rates were significantly lower in patients with a documented history of diabetes (6.8% versus 13.4%, p<.001) as was the proportion of survivors with good (eGOS ≥7) neurological outcome (41.6% versus 60.4%, p=.002). Median prehospital blood glucose levels were higher in patients who achieved ROSC versus those who did not (10.4 mmol/l versus 7.2 mmol/l, p<.001). In multivariate analysis, the presence of diabetes was associated with a significant reduction in the odds of survival to hospital discharge in cases presenting in a shockable rhythm (OR 0.57, 95% CI 0.38-0.86, p=.007) but not when the rhythm was non-shockable (OR 1.01, 95% CI 0.72-1.43, p=.95). In contrast to previous studies, patients with mild (8.0-11.9 mmol/l) and moderate (12.0-15.9 mmol/l) hyperglycaemia demonstrated significantly higher odds of survival to discharge (OR 2.2, 95% CI 1.5-3.2 and OR 1.8, 95% CI 1.2-2.7 respectively) and good neurological outcome at 12-months (OR 2.1, 95% CI 1.3-3.4 and OR 1.9, 95% CI 1.1-3.3), although these results should be interpreted with caution given the limited sub-group of patients in whom prehospital blood glucose was recorded. This may also be reflective of the more clinically heterogenous resuscitation population from which this sample was obtained, compared with the exclusively witnessed shockable cardiac arrest cases analysed by Nurmi et al. (2012).

4.13.1 Summary

Derangements in blood glucose are associated with worsened outcomes in several studies, however the risks of implementing strict glycaemic control are also highlighted. In most UK ambulance services blood glucose is routinely measured using point of care capillary blood samples. Some evidence suggests that single prehospital blood capillary glucose measurements in isolation are inadequate and that monitoring of longer-term trends in blood glucose is required for accurate prognostication. The apparent association between diabetes and worsened outcome in some studies is also an important factor to consider as part of pre-planned analysis.

4.14 Overall summary

Multiple demographic, clinical and EMS system-based factors have the potential to influence survival and neurological outcome in cardiac arrest (Sasson et al., 2010). Some variables, such as performance of bystander CPR, presence of a shockable rhythm, shorter response times and early defibrillation, are unequivocally associated with improved survival and therefore form part of the Utstein template international reporting standards for out-of-hospital cardiac arrest (Perkins et al., 2015). In other cases, established therapeutic interventions for cardiac arrest such as administration of adrenaline and initiation of mild therapeutic hypothermia have been called into question as new evidence emerges. Other factors appear to have some association with outcome, such as gender, however the evidence remains equivocal and direct causation unproven. This is a situation which pertains equally to airway management in out-of-hospital cardiac arrest and therefore accounting for the potential for multiple confounders is an important aspect of statistical analysis in observational cardiac arrest research.

4.15 Implications for the current Study

This section has reviewed international evidence relating to factors influencing survival following out-of-hospital cardiac arrest. In keeping with research relating to the influence of airway management on outcome, studies examining other factors associated with mortality and morbidity in out-of-hospital cardiac arrest employ a variety of methodological approaches encompassing a range of heterogenous populations. Variations in both prehospital and in-hospital management regimens across geographical and service boundaries frequently limit the extent to which study findings are directly applicable to UK systems of care. The importance of trends rather than isolated values in physiological measurements such as blood pressure, $ETCO_2$ and temperature is illustrated in a number of studies, highlighting the importance of recording data from the in-hospital phase of care against which prehospital records may be compared. Accessing data from multiple sources in this fashion may raise appreciable information governance and ethical issues.

There are a number of well-established factors, such as the presence of a shockable rhythm and provision of bystander CPR, known to significantly influence outcome following cardiac arrest. These are relatively straightforward and frequently form part of standardised reporting formats such as the Utstein template. Other factors are established predictors of survival but are not consistently collected, such as time to ROSC. This is an important measure which cannot be accounted for in a number of large-scale registry analyses but is likely to be feasible within the host EMS system. Further research challenges are posed by factors where there is an apparent association with outcomes but evidence remains equivocal, especially where this challenges conventional wisdom in resuscitation medicine. The controversy surrounding the administration of adrenaline and the initiation of therapeutic hypothermia versus targeted temperature control are clear examples of this. These factors present particular challenges in the context of non-randomised observational research, where epidemiological approaches including techniques such as logistic regression are reliant on accounting or controlling for confounding factors. Where these factors remain poorly understood, the reliability and validity of statistical models that incorporate them may be questioned. It is therefore vital that the overview of factors affecting survival contained within this section is used to guide and inform data collection methods, study methodology and analysis of results in subsequent chapters.

5. Methodology

5.1 Introduction

Defining the methodological approach is a key stage in developing a programme of research, which necessitates progression from broad assumptions to detailed methods of data collection, analysis and interpretation (Creswell, 2014). The process of research is ultimately undertaken within a framework of a set of philosophies using procedures, methods and techniques that are both valid and reliable and designed to be unbiased and objective (Kumar, 2011). Decisions relating to the specific research approach are informed by the study setting, procedures of inquiry or research design, specific methods of data collection, analysis and design, and the nature of the research problem (Creswell, 2014). The following section describes the study setting and the processes and rationale underpinning the final study design and methodological approach.

5.1.1 Study aim and objectives

As stated previously, the overall aim of the study is to examine the effect of different airway management strategies on outcomes in patients who suffer out-of-hospital cardiac arrest and, after treatment by the ambulance service, regain a pulse and undergo direct transfer to a specialist Heart Attack Centre.

The methodological approach will be designed to achieve the associated objectives, which are defined as follows

- To investigate clinical and demographic variables that may influence outcome
- To investigate the hospital course including clinical management and final neurological and mortality outcomes for this cohort.
- To investigate any variation in physiological data (such as heart rate) between patients treated using different airway management techniques.
- To investigate the type of airway management approach employed in relation to patient demographics (such as age or gender).

5.2 Study setting

The London Ambulance Service (LAS) National Health Service (NHS) Trust is the largest free-at-the-point-of-access emergency ambulance service in the world, serving a population of 8.2 million people distributed throughout an area of 1,579 km^2 (Fothergill et al., 2013). Within the UK, Emergency Medical Services (EMS) are provided by NHS Ambulance Trusts accessed via the universal 999 emergency number. Incoming calls are triaged via clinical assessment software based on algorithms and a response category assigned with pre-arrival telephone advice provided by emergency medical dispatchers where required (Black & Davies, 2005). Clinical care is provided by Emergency Ambulance Crew (EAC) and Emergency Medical Technicians (EMT) trained in intermediate life support, including the use of supraglottic devices such as the laryngeal mask airway and i-gel in some cases, and Paramedics trained in Advanced Life Support (ALS) including but not limited to manual defibrillation, advanced airway management, administration of a range of parenteral drugs, and interpretation of 12 lead electrocardiograph (Soar et al., 2013). In March 2012 the LAS introduced the i-gel as the preferred SGA device for use by ambulance clinicians.

Paramedics form part of the response to most 999 calls within UK ambulance services (Black & Davies, 2005), unlike other EMS systems globally where higher acuity calls may be supplemented by an additional tier of more highly qualified and experienced paramedics (Trevithick et al., 2003; Pozner et al., 2004; Symons & Shuster, 2004; MacFarlane et al., 2005). Since 2011, patients attended by the LAS with ROSC and electrocardiographic evidence of STEMI or new onset Left Bundle Branch Block (LBBB) following out-of-hospital cardiac arrest undergo direct transfer to specialist HACs equipped to provide primary PCI (PPCI) and post ROSC care (Iqbal et al., 2015). These referrals are made autonomously by paramedics and other ambulance clinicians directly from the scene of the incident on the basis of interpretation of the prehospital ECG and clinical presentation (Fothergill et al., 2014).

5.3 Rationale for methodological approach

The process of formulating the study design reflects the priority given to a range of dimensions within the research process (Bryman, 2012). Historically, researchers have been faced with a dichotomous choice between qualitative and quantitative methods, although mixed methods approaches have also gained acceptance (Tashakkori & Teddlie, 2010). Traditionally, qualitative and quantitative approaches are considered as distinct entities. An alternative perspective is that these paradigms represent different ends on a continuum, and that studies tend to be more quantitative than qualitative and vice-versa (Creswell, 2014). Ultimately, the methodological approach employed is determined by the research question (Kumar, 2011).

In the context of the stated research question and associated objectives, a quantitative approach designed to quantify the magnitude of difference associated with any observed variation in clinical outcomes according to airway management approach was considered appropriate. Randomised Controlled Trials (RCTs) and meta-analyses of multiple RCTs traditionally occupy the highest positions within the hierarchy of evidence, and are often considered the most reliable means of determining the effect of a given treatment or intervention (Moore & McQuay, 2006). However, RCTs commonly require large sample sizes, established mechanisms for randomisation and blinding, and may not be conducted for a sufficient period to measure long term or adverse events (Peat, 2002). Appreciable financial and logistical resources are usually required to conduct RCTs, and very significant ethical issues may arise from the process of randomisation in cases where participants receive different treatments or are denied an intervention altogether (Brink & Wood, 1998). Furthermore, the varying skill levels of ambulance clinicians attending the patient group outlined above would render it difficult to achieve consistent randomisation as not all providers are capable of performing the full range of airway interventions under consideration. Given these challenges, an RCT was not considered an appropriate or achievable method for addressing the primary research question.

The study population comprises participants who share the characteristics of ROSC post cardiac arrest and direct transfer to a regional HAC. During initial resuscitation and ongoing management, participants within this group were exposed to different airway management approaches. Although it was not feasible to randomise participants to receive different airway management approaches due to the logistical challenges and variations in provider skillset outlined earlier, it was possible to obtain data at various stages throughout the patient journey. This, coupled with the need to quantify any observed differences between different airway management approaches, rendered the study eminently suited to the use of epidemiological methods, specifically a prospective longitudinal cohort approach (Creswell, 2014). Cohort studies typically measure the occurrence of disease over a period of time in one or more groups with shared characteristics (Rothman, 2012). In this instance participants are characterised by entry to the regional HAC system after prehospital ROSC. Mortality and neurological outcome constitute the disease patterns of interest, with variation in exposure to airway management approach defining cohorts for comparison.

Consideration was given to the use of case-control methodology, whereby cases exposed to the disease of interest are compared with non-exposed controls (Peat, 2002). In terms of study populations, controls are generally selected independently of cases which would not have been possible given the sampling approach taken in the current study. Furthermore, there would have

been a requirement to match cases exposed to endotracheal intubation to controls managed via a supraglottic device and it was not known at the outset whether the proportions of patients undergoing these techniques would permit such comparisons. Statistical power of such studies can be increased if matching techniques are used to match multiple controls to a single case, however this is reliant on an adequate population from which controls may be recruited (Peat & Barton, 2014). Such methodological approaches render case-control studies prone to bias and unable to provide valid estimates of risk, hence they tend to occupy a lower position in established hierarchies of evidence than those based on longitudinal observational approaches (Woodward, 2014). In view of this, case-control methodology was rejected in favour of a prospective observational cohort approach.

Cohort studies may be conducted prospectively or retrospectively. Advantages associated with retrospective approaches include immediate access to the required data and elimination of the Hawthorne effect, whereby behaviour may be altered as a consequence of research being conducted (Peat, 2002). However, such approaches do not permit further investigation or follow up beyond that which has already been conducted, and often rely on the use of data not primarily collected for research purposes, raising issues over reliability and completeness (Creswell, 2014). In contrast, whilst prospective longitudinal approaches require longer study periods to collect sufficient data, these data are collected as part of a research process and additional follow up of subjects and further assessment of health status are feasible (Rothman, 2012). Although a proportion of the required dataset could have been acquired through retrospective review of ambulance and hospital records, this approach would have excluded more comprehensive and reliable assessment of neurological function over time, which was a core research objective and provides unique post event data relating to physical and mental functioning in addition to clinical and physiological variables alone (Bowling, 2005). Accessing archived data and obtaining informed consent to review identifiable clinical data are also challenges associated with retrospective studies involving clinical notes and may result in incomplete data and recruitment bias (Bryman, 2012).

5.4 Study design

The study design was therefore based upon a prospective longitudinal cohort approach incorporating three main phases of data collection throughout the patient journey:

1. Prehospital treatment and transfer phase – review of ambulance service patient report form (PRF) data to determine patient demographics, key timings (response time, timing of interventions, transfer times), airway management strategy, therapeutic interventions and receiving HAC.

2. Heart attack centre initial management and ongoing in-patient treatment, including in-hospital mortality, clinical course and associated interventions derived from review of hospital records.

3. Assessment of mortality and neurological outcome at discharge via the CPC scale. For neurologically intact survivors (CPC 1&2), administration of the SF36 health survey at 90-120 days post discharge to provide more comprehensive assessment of physical and mental health components.

5.5 Study sites

The sites participating in the study following local research and development approval were as follows:

- London Ambulance Service NHS Trust (prehospital and survivor follow up phases)
- London Regional Heart Attack Centres (In-hospital phase only)
    - The Heart Hospital, University College London Hospital NHS Foundation Trust
    - The London Chest, Barts and The London NHS Trust
    - Harefield Hospital, Royal Brompton and Harefield NHS Foundation Trust
    - Royal Free Hospital, Royal Free Hampstead NHS Trust
    - St Thomas' Hospital, Guy's and St Thomas' NHS Foundation Trust
    - Kings College Hospital NHS Foundation Trust
    - Hammersmith Hospital, Imperial College Healthcare NHS Trust

5.6 Participants

Potential participants were identified through the London Ambulance Service NHS Trust via existing cardiac arrest registry data collection procedures and their subsequent progress through the healthcare system tracked via the receiving hospital NHS Trust. Patients were eligible for inclusion in the study if all of the following criteria were fulfilled -

1. Patient aged 18 years or above suffering prehospital cardiac arrest

2. Return of spontaneous circulation (ROSC) achieved

3. Active airway management employed during resuscitation efforts

4. Patient transferred directly by London Ambulance Service Staff to specialist regional heart attack centre as per existing service protocols

Patients were excluded from the study in the presence of any of the following:

1. Cases where responsibility for prehospital airway management fell to a practitioner other than an LAS ambulance clinician (e.g. Prehospital physician)

2. LAS witnessed VF arrest with immediate defibrillation and successful cardioversion requiring no active airway management and no delivery of intermittent positive pressure ventilation post ROSC

3. Cardiac arrests where no active airway management and intermittent positive pressure ventilation were performed (e.g. patients with ROSC after delivery of chest compressions alone with no requirement for airway management post ROSC)

5.7 Outcome measures

The International Liaison Committee on Resuscitation (ILCOR) consensus recommendations provide a framework for the range of variables to be recorded in cardiac arrest research and audit (Figure 1). In addition to the requirement to record key timings, patient demographics and clinical and physiological data, it is suggested that assessment of neurological outcome should form a core part of routine data collection with longer term quality of life measures regarded as supplemental data (Perkins et al., 2015). A variety of standardised measures exists through which health outcomes may be measured. These range from relatively straightforward systems of categorisation based on clinical and functional measures such as mortality or cognitive impairment to more sophisticated and extensive methods of assessing quality of life, usually incorporating patient reported data across a range of physical and mental health domains (Mak, Moulaert, Pijls, & Verbunt, 2016). ILCOR guidance on assessment of neurological outcome recommends the use of either the Cerebral Performance Category (CPC) or Modified Rankin Scale (mRS). No further guidance is offered in relation to appropriate longer term survival or quality of life measures (Perkins et al., 2015).

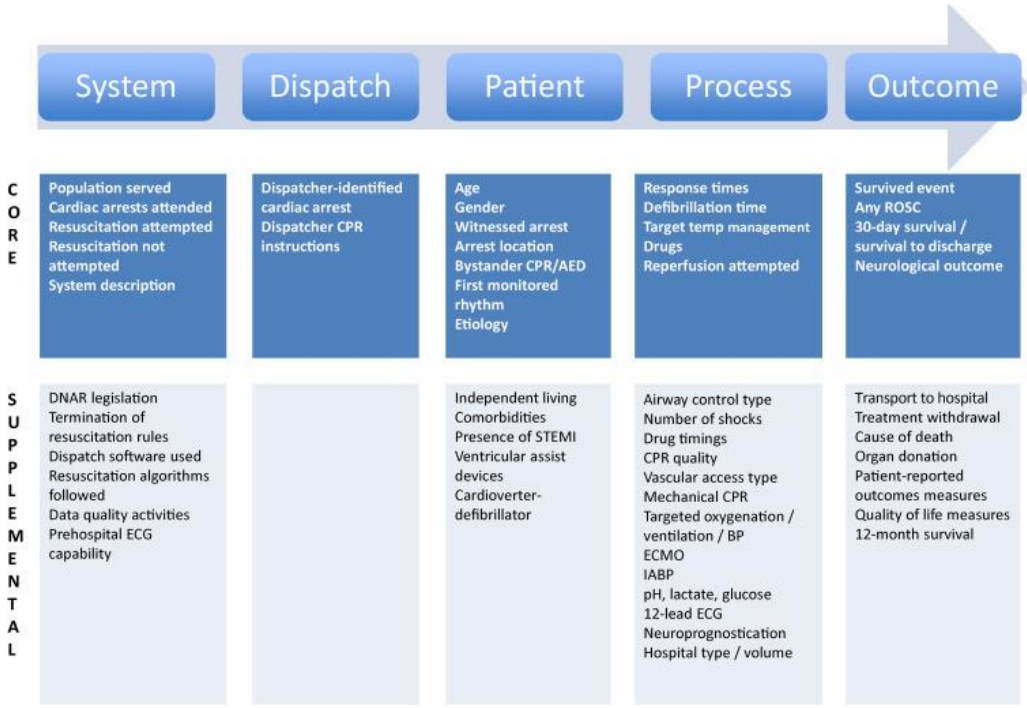

Figure 1 Core and supplemental data domains as recommended by the International Liaison Committee on Resuscitation (Perkins et al 2015)

The mRS is a 7-point scale ranging from 0 (no symptoms) to 6 (dead), whereas the CPC scores cerebral and functional status on a five-point scale, ranging from 1 (good cerebral performance) to 5 (brain death) (Rittenberger et al., 2011). A comparison of these scales is shown below (Table 9). ILCOR guidance defines survival with favourable neurological outcome as CPC category 1 or 2 or mRS 0 to 3 (Perkins et al., 2015). Both have been used to assess outcome in survivors of out-of-hospital cardiac arrest and may be calculated through review of patient notes (Herlitz et al., 1995; Abe, Tokuda, & Ishimatsu, 2009; Haukoos et al., 2010; Rittenberger et al., 2011; Winther-Jensen et al., 2015).

Table 9 Comparison of criteria for Modified Rankin Scale and Cerebral Performance Category

Score	mRS	CPC
0	No symptoms at all	
1	No significant disability despite symptoms, able to carry out all usual duties and activities	Good cerebral performance – conscious, alert, able to work, might have mild neurological or psychological deficit
2	Slight disability, unable to carry out all previous activities but able to look after own affairs without assistance	Moderate cerebral disability – conscious, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment
3	Moderate disability, requiring some help but able to walk without assistance	Severe cerebral disability – conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis
4	Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance	Coma or vegetative state – any degree of coma without the presence of all brain death criteria. Unawareness even if appears awake without interaction with environment. May have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness
5	Severe disability, bedridden, incontinent and requiring constant nursing care and attention	Brain death
6	Dead	

Neither the mRS nor the CPC were originally designed for use in cardiac arrest research. The original Rankin scale was developed in 1957 to assess disability in acute stroke patients (Rankin, 1957), and subsequently modified to suite the requirements of researchers examining the use of aspirin in transient ischaemic attack (Farrell, Godwin, Richards, & Warlow, 1991). The CPC scale was developed later in the mid 1970's to provide a straightforward means of categorising outcome following severe brain damage (Jennett & Bond, 1975). Despite this, CPC has been described as the standard outcome measure in cardiac arrest (Raina, Callaway, Rittenberger, & Holm, 2008). In a recent systematic review of outcomes reported in cardiac arrest clinical trials, CPC at discharge was the most frequently reported measure (n=14, 23%), with a further seven studies (11%) employing CPC variants such as the Glasgow Pittsburgh CPC score (Whitehead, Perkins, Clarey, & Haywood, 2015). In contrast, the mRS was used as an outcome measure in only three studies incorporated as part of this review.

Critics of the CPC assert that the scale has historically been poorly defined and not subject to appropriate validation, including comparison with more sophisticated health outcome measures.

The use of retrospective chart review and an emphasis on discharge destination are also highlighted as potential weaknesses alongside concerns regarding inter-rater reliability (Hsu, Madsen, & Callaham, 1996). One retrospective chart review of North American survivors of out-of-hospital cardiac arrest (n=211) found a fair relationship between the CPC and mRS (tau 0.43) and poor relationships between CPC and discharge disposition (tau 0.23) and mRS and discharge disposition (tau 0.25), concluding that individual instruments provided wildly differing estimates of good outcome (Rittenberger et al., 2011). Discharge destinations included home with no services, home with home healthcare, acute rehabilitation facility, skilled nursing facility, long term acute care facility, and hospice. Multiple factors can affect discharge destination, including social circumstances, relationship and family status, financial means and local availability of services, suggesting that discharge destination may not be a reliable outcome measure in isolation (Rittenberger et al., 2011). A smaller North American study compared CPC and mRS scores calculated at discharge with mRS, CPC and in-person Health Utilities Index Mark 3 (HUI3) quality of life scores derived from face-to-face interviews with cardiac arrest survivors (n=21) one month post hospital discharge following cardiac arrest (Raina et al., 2008). Substantial variation in discharge and one-month mRS and HUI3 scores were identified within each CPC category. In addition, CPC scores at discharge were significantly better than those at one month, thus overestimating longer term cognitive and disability status.

In contrast, a retrospective review of a subset of survivors of cardiac arrest who received targeted temperature management found that CPC 1 survivors had the highest long-term survival followed by CPC 2 and 3, with CPC 4 having the lowest long-term survival ($p < .001$), and concluded that CPC score is a reliable predictor of long term outcome (Hsu et al., 2014). This study sample comprised survivors of both in and out-of-hospital cardiac arrest and only assessed CPC as an outcome predictor in those undergoing targeted temperature management (24%, n=144) which has been demonstrated to produce superior neurological outcomes (Nielsen et al., 2013; Nielsen, Wetterslev, & Friberg, 2014; Cronberg et al., 2015). Comparison of CPC scores with the HUI3 as part of the renowned Ontario Prehospital Life Support (OPALS) series of studies found that a CPC score of 2 or 3 ruled out good quality of life (HUI3 > 0.80), with a sensitivity of 100% (95% CI 98% - 100%) and specificity of 27.1% (95% CI 20% - 35%) (Stiell et al., 2009). When the CPC was 1 it was highly unlikely that health would be poor, therefore the CPC was able to predict poor quality of health (Health Utilities Index >0.40) with a sensitivity of 55.6% (95% CI 42% - 67%) and specificity of 96.8% (95% CI 94% - 98%). This was a larger prospective observational study (n=305) exclusively addressing outcomes in survivors of out-of-hospital cardiac arrest managed by Canadian EMS. The authors

conclude that whilst the CPC is not a substitute for more sophisticated quality of life measurements, it can indicate broad functional outcome categories that are useful for a number of key clinical and research applications. In the context of the current study, the implication is therefore that the relatively crude classifications of neurological outcome offered by scales such as the CPC are valid within the constraints discussed above, but need to be supplemented by more sophisticated health outcome measures to ensure adequate assessment of long-term outcomes.

Determining the most appropriate outcome measure in the context of the specific resuscitation population under consideration is therefore problematic. ILCOR recommendations imply that both scales are equally acceptable for reporting neurological outcome but offer no further guidance regarding the relative merits of each. Despite concerns regarding inter-rater reliability and variation in estimates of good outcome when compared with other instruments, CPC scoring has been shown to be a reliable predictor of long term outcome and is identified as the most commonly used measure of outcome in cardiac arrest trials (Hsu et al., 2014; Whitehead et al., 2015). Use of CPC scoring would therefore permit more direct comparison of the results of this research with the majority of studies employing similar methodology, thus enhancing external validity and generalisability (Peat, 2002). In addition, CPC scoring is commonly employed in studies specifically investigating the association of airway management approach with outcome in cardiac arrest, which is of particular importance in the context of the research question under consideration (Nagao et al., 2012; Hasegawa et al., 2013; Tanabe et al., 2013; McMullan et al., 2014). In cases where a single reviewer calculates CPC scores, a satisfactory level of intra-relater reliability has been noted (Rittenberger et al., 2011). It is therefore possible to ameliorate these concerns by using a single reviewer to determine CPC from retrospective chart review and augmenting CPC discharge scores with an appropriate quality of life assessment tool administered post discharge. On this basis, CPC scoring was determined to be the most appropriate instrument for assessment of neurological outcome at discharge, with the caveat that further post discharge assessment of outcome would be undertaken via an appropriate quality of life measure.

The assessment of longer term outcomes in cardiac arrest survivors via quality of life measures is regarded as supplemental data by ILCOR (Perkins et al., 2015), but may be important given the limitations associated with less sophisticated measures such as CPC scoring (Hsu et al., 1996). Longitudinal measurement of CPC scores is undertaken in some studies and may permit more reliable assessment of longer term outcomes. However, relatively few cardiac arrest outcome studies employ more sophisticated quality of life measures (Whitehead et al., 2015), the

administration of which poses significant logistical and ethical challenges in this patient group (Perkins et al., 2015).

A systematic review of quality of life and other patient reported measures in out-of-hospital and in-hospital cardiac arrest survivors found that studies used a range of validated assessment measures and bespoke tools including un-validated questionnaires and structured interviews (Elliott, Rodgers, & Brett, 2011). The most commonly used validated instruments were the Health Utilities Index 3 (HUI3), SF-36 survey and the EQ-5D. The HUI3 employs utility scoring using five or six levels in eight domains referred to as attributes (vision, hearing, speech, ambulation, dexterity, cognition, emotion and pain) and may be administered to those aged five years and over. Potential scores range from -0.36 to 1.0, with -0.36 representing the worst possible health state and 1.0 representing perfect health (Horsman, Furlong, Feeny, & Torrance, 2003). HUI3 questionnaires can be both self-completed or interviewer administered and can also be completed by proxy, providing the potential for inclusion of quality of life outcomes for survivors of cardiac arrest whose level of neurological impairment or state of health might otherwise exclude them from participation (Elliott et al., 2011). The SF36 contains 36 items measuring eight dimensions of physical and mental function. It is now the most frequently used measure of generic health status globally, permitting comparison of study results with established population norms and other studies employing similar methodology (Bowling, 2005). The SF36 survey may also be administered via a variety of means, including self-administration, on-line administration, structured interview and via telephone. Evidence suggests that telephone administration is of equivalent validity to self-administration (Garcia et al., 2005). The EQ5D is primarily designed for self-completion by respondents and may be used in postal surveys, clinics or face-to-face interviews. It measures self-reported health and functional outcomes in five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with three standard response options for each domain (no problems, some problems, extreme problems) (Szende & Williams, 2004).

There are a number of challenges and considerations associated with selection of an appropriate quality of life instrument in the context of a geographically diverse population of cardiac arrest survivors whose in-hospital management and therefore clinical records are distributed throughout a regional system of centralised heart attack centres. Given the evidence that CPC scoring at discharge may overestimate the prevalence of favourable neurological outcome (Rittenberger et al., 2011), the most pressing need for more sophisticated quality of life health outcome assessment post discharge arguably rests with participants categorised as having favourable neurological outcome as

per ILCOR definitions (CPC 1 & 2). Identifying more subtle variation in physical and mental health in this sub-set of patients post discharge is likely to be of particular importance in determining the potential influence of airway management strategy on longer term outcomes. Financial and logistical constraints associated with the programme of research are also important considerations in determining the appropriate method of administration of any quality of life measure. The need to assess longer term outcomes dictates that administration of any instrument would occur in the post discharge phase. There is potential for wide geographical distribution of survivors judged to be neurologically intact, with the result that face-to-face administration is unlikely to be consistently feasible, especially where a lone researcher remains responsible for data collection. Poor response rates are often seen in postal surveys, therefore this was discounted as an option (Bryman, 2012). In view of this, the SF36 Health Survey was selected as the most appropriate long-term quality of life measure on the basis that it is regarded as the most frequently used measure in health research, is commonly employed in cardiac arrest research, and may be administered via structured telephone interview.

5.8 Sample size

Sample size calculations were performed using the G* Power freeware programme (Faul, Erdfelder, Lang, & Buchner, 2007; Faul, Erdfelder, Buchner, & Lang, 2009) with statistical significance set at $p < .05$ and power (1-beta) of 0.8 based on contingency table analysis (Chi Square) using Cohen's effect sizes (Warner, 2013). On the basis of four distinct airway management approaches (basic management only, supraglottic airway insertion, endotracheal intubation or a combined approach) with initial outcomes stratified according to the five-point Cerebral Performance Category scale, a sample of 193 patients would be required to detect a medium effect size. This sample size was increased by approximately 10% (n=220) to allow for patients lost to follow-up based on experiences from a prior Australian RCT (Bernard, Nguyen, et al., 2010) addressing paramedic airway management in trauma, where patients were randomised to either Rapid Sequence Intubation (RSI) or standard airway management in the presence of traumatic brain injury with neurological outcomes assessed at 6 months. In the Australian study (Bernard, Nguyen, et al., 2010), increasing the sample size by 20% to detect a one point change in extended Glasgow Outcome Scale (eGOS) to achieve 80% power and alpha error 0.05 yielded a sample size of n=312. However, ultimately only 4% of patients were lost to follow up and therefore an increase of approximately 10% above the a priori sample size calculation in the current study was felt to be appropriate using the same power and significance level as the Australian RCT (Bernard, Nguyen, et al., 2010).

At the time of sample size calculation, information from the London Ambulance Service Clinical Audit and Research Unit indicated that 10-15 patients per month would meet the study inclusion criteria. Assuming a maximum data collection period of two years, this sample size was felt to be feasible. Using the same calculation, recruitment of sufficient participants to enable detection of a small effect would require a sample size in excess of 1,700 patients, which was not feasible given the time constraints and resources involved. A large effect could be detected with 70 patients and therefore consideration was given to the need for an interim review when recruitment reached this level. A further sample size calculation using G* Power based on one-factor Analysis of Variance using Cohen's effect sizes indicated that 180 participants would be required to detect a medium effect size when comparing SF-36 Health Survey results between different airway management approaches. The same significance level and power values detailed earlier were applied to these calculations, thus indicating that the sample size discussed above would be sufficient to detect a medium effect for all pre-planned statistical analyses.

5.9 Data collection procedure

The LAS Clinical Audit and Research Unit (CARU) Cardiac Data Officer provided the researcher with a monthly report detailing cases fulfilling study criteria. These data were extracted from an existing dataset based on established Trust reporting and archiving mechanisms. On receipt of these cases, the researcher added records to a separate study specific database and gathered further data from the ambulance service phase of care for individual cases via the electronic call log and associated Patient Report Form (PRF). Once sufficient data had been obtained from LAS records, the researcher contacted the relevant HAC to determine the location of the patient and enable the clinical course to be monitored. At the point of death or discharge from hospital care, the researcher contacted the relevant HAC to request review of the clinical notes.

The researcher visited each Heart Attack Centre at regular intervals as dictated by the number of eligible cases received. For each case, hospital records were reviewed and relevant clinical information extracted for entry into the study specific database. For cases where death occurred prior to hospital discharge, the researcher determined the location of the patient at the time of death and annotated the study database record accordingly. In cases where the patient was discharged to another hospital site, the researcher similarly annotated the study record accordingly. No further follow up was possible at other hospital sites where ethical approval had not been granted.

Survivors determined to be neurologically intact (CPC 1&2) received a study information pack by post, consisting of a participant information sheet (appendix 1), letter from the relevant lead HAC

consultant (appendix 2), and consent form (appendix 3). Participants were invited to consent as per the terms of ethical approval to the use of clinical data already obtained and to further follow up in the form of telephone administration of the Short Form 36 (SF36) survey (QualityMetric ©) at a mutually convenient time between 90 – 120 days post hospital discharge. In cases where survivors were judged to have significant neurological impairment (CPC 3-5), the closest relative or other representative noted in the clinical records received an alternative study information pack, providing similar information and documents modified for consideration by a consultee (appendix 4) acting under the auspices of the Mental Capacity Act 2005 (Bartlett, 2005). In these cases, the consultee was asked to provide an opinion as to whether the patient would have wished to consent to use of their data as part of the study. In the event that the consultee indicated that the patient would likely have agreed to the inclusion of their data, or no response was received from the consultee, physiological data relating to that case was retained. In the event that the consultee indicated that the patient would not have wished to participate, any data relating to that patient was destroyed. In all cases where no response was received, a single follow up phone call was made to each potential participant or consultee and one further study information pack posted if appropriate. After this, no further follow up was attempted. In cases where the patient died prior to discharge, ethical approval was granted to retain clinical data without recourse to the closest relative or other consultee. A simplified representation of data flow is shown below (Figure 2).

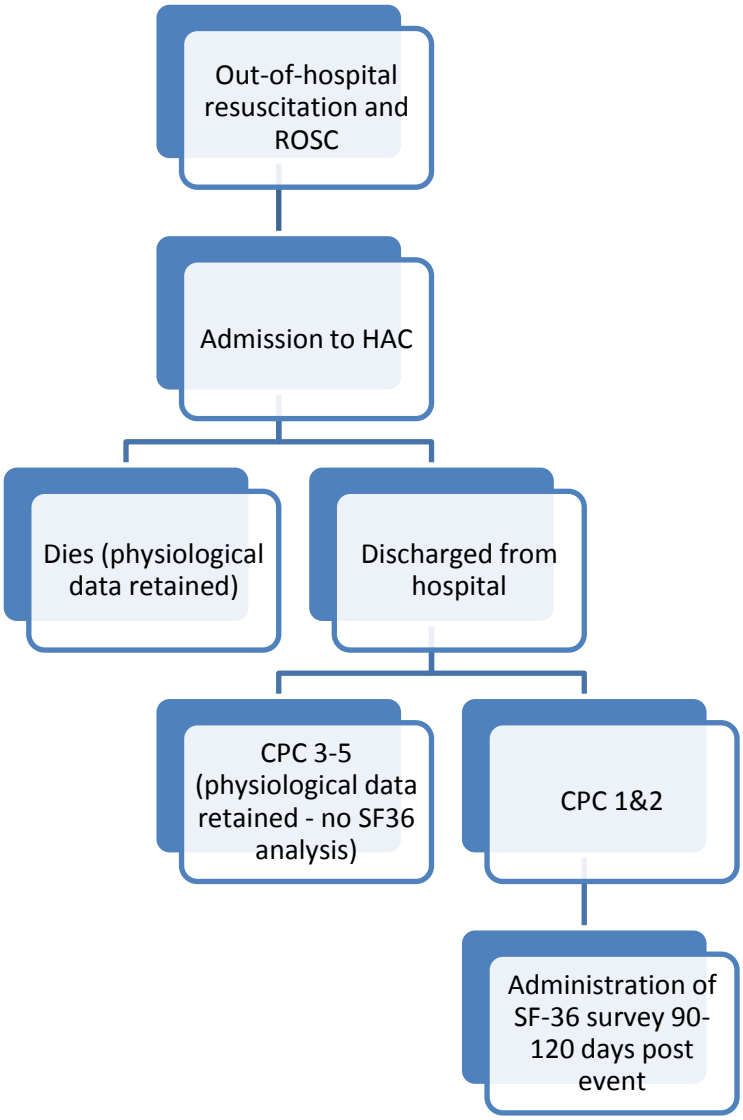

Figure 2 Simplified study data flow

5.10 Statistical analysis

Data analysis was performed using IBM SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Statistical analysis of study data was progressed through a range of phases employing descriptive statistics, measures of association such as chi-square testing and calculation of odds ratios, through to binomial logistic regression. Patient demographics and key clinical and physiological data were initially quantified using descriptive statistics including measures of central tendency (mean, median and mode) and measures of dispersion (standard deviation and range) as appropriate. This phase of the analysis was designed to examine the data distribution of key variables. At the outset, it was determined that the use of non-parametric statistics would be appropriate on the basis that several key variables constituted nominal or ordinal data and a number of other ratio and interval variables exhibited non-normal distribution (Petrie & Sabin, 2009).

Subsequent analyses were performed with statistical significance set at $p < .05$ throughout (Riffenburgh, 2006). Initial analysis was undertaken with outcome data grouped into a binary classification of good (CPC 1&2) versus poor (CPC 3-5) neurological outcome as per ILCOR definitions (Perkins et al., 2015). Chi-square testing was employed to examine differences in clinical and demographic categorical variables, firstly between the study sample with complete data available for analysis versus those lost to follow-up (e.g. transferred to a non-participating hospital) and secondly between participants from different airway management groups (Field, 2013). Comparison of distribution for demographic and clinical variables constituting interval and ratio data was undertaken using the Mann Witney U test (Warner, 2013). This approach to analysis of categorical variables was then repeated with outcome data stratified by individual Cerebral Performance Category (CPC) score. On the basis that the CPC scores constitute ordinal data, the Kruskal-Wallis test was used to compare distributions for interval and ratio data across the full range of CPC categories (Field, 2013). The final stage of this phase of analysis planned to compare SF-36 Health Survey scores between the different airway management groups and CPC outcome groups via Analysis of Variance (ANOVA) testing, on the proviso that these scores were normally distributed (Petrie & Sabin, 2009).

Unadjusted and adjusted odds ratios were calculated to quantify the odds of good versus poor neurological outcome according to whether the patient was exposed to airway management via a supraglottic device or endotracheal tube (Petrie & Sabin, 2009). These analyses were performed for all cases and then repeated for cases presenting in shockable and non-shockable (asystole and PEA) rhythms. Existing studies have observed significant differences in the odds of survival associated

with specific airway management devices according to whether the initial presenting rhythm in cardiac arrest was shockable versus non-shockable (Egly et al., 2011). Adjusted odds ratios were calculated as part of the logistic regression procedures described below (Warner, 2013).

In the final phase of statistical analysis, binomial logistic regression techniques were employed to construct models to predict outcomes stratified by good (CPC 1&2) versus poor (CPC 3-5) outcome. This modelling was conducted in two stages, the first incorporating variables identified as significant predictors of outcome from this dataset and the second incorporating standard variables conventionally associated with survival in the wider resuscitation literature. The various stages of logistic regression were performed using a blockwise approach to specify the models, entering potential predictor variables systematically in order to determine the best fit in accordance with the principle of parsimony (Field, 2013).

5.11 Rationale for statistical approach

Neurological outcome measures and some associated clinical and demographic data, such as gender, airway management approach and presenting rhythm, constitute categorical variables (Field, 2013) that are central to the primary research question. Quantifying the significance of any variation in the incidence of a given dependent variable between groups exposed to different airway management approaches is therefore a key aspect of planned statistical analyses. The chi square test indicates whether there is a significant difference in the incidence of a given characteristic between subgroups within a sample (Peat, 2002). Data for chi square test calculations are initially obtained as frequencies, defined as the numbers with and without the characteristic of interest. These data are then presented in contingency tables to examine whether the proportions of participants who possess the characteristic of interest are the same between different groups. The expected frequency is the product of the two marginal totals divided by the overall total. A discrepancy between the observed and expected frequencies provides an indication that the proportions within the groups differ. The test statistic provides a measure as to whether this discrepancy is of statistical significance (Petrie & Sabin, 2009).

The chi square test is based on an approximate distribution, which is inaccurate where the sample size is small or 2x2 contingency tables are used (Argyrous, 2011). Conventionally, where expected frequencies are greater than five, the sampling distribution of the Pearson chi square test is regarded as satisfactory. Expected frequencies below this level generally indicate a small sample size which renders the sampling distribution of the Pearson chi square test too deviant from the standard chi square distribution to be reliable (Field, 2013). Under these circumstances Fisher's exact test should be employed (Peat, 2002), which computes the exact probability for the Chi Square

statistic and is therefore more reliable in the presence of smaller sample sizes (Field, 2013). In addition, continuity-corrected chi square testing for 2x2 tables provides a more conservative and therefore less significant value than Pearson's chi square (Peat, 2002).

Parametric tests are based on a priori knowledge of the probability distributions that the data follow. Non-parametric tests, also referred to as distribution free or rank methods tests, are not reliant on the assumption that data are normally distributed (Petrie & Sabin, 2009). The principle underpinning non-parametric approaches is that numerical data values are placed in ascending order and then given a score commencing from one for the lowest ranked value continuing sequentially until the highest value is scored. Where the same numerical value occurs multiple times then the value is assigned a rank that is an average of the potential rank for these scores – this is referred to as a tied rank. Individual ranked scores are then summed to provide a total for each group of interest (Field, 2013). If the distributions of data values are comparable then the expectation would that the summed ranks would also be similar for each group.

Where there is a requirement to assess difference in mean values between two independent groups, the parametric t-test is conventionally used. This is contingent upon the variable of interest being normally distributed in each group (Riffenburgh, 2006). The Mann-Whitney test constitutes a non-parametric equivalent of the t-test and does not require that assumptions of normal and equal variances are met (Field, 2013). Similarly, the non-parametric Kruskal-Wallis test may be employed where there is a requirement for comparisons of multiple groups and it would be inappropriate to use parametric tests such as analysis of variance (ANOVA) (Petrie & Sabin, 2009). Non-parametric tests are generally regarded as less powerful and more prone to type 2 error than equivalent parametric tests. However, their use is appropriate in the context of distributions that violate assumptions of normality and smaller sample sizes.

Several measures of association may be used in observational research to estimate the risk of an outcome occurring, including the relative risk (RR) and odds ratio (OR) (Peat, 2002). The RR is the proportion of subjects with the outcome of interest in the exposed group divided by the proportion in the non-exposed group whereas the OR is the odds of exposure in the group with the outcome of interest compared with the odds in the non-exposed group (Riffenburgh, 2006). In the context of the current study, the airway management approach constitutes the exposure of interest and neurological status the outcome measure. Despite apparent similarities between these measures, the OR only closely approximates to RR in circumstances where the exposure of interest is rare. Under other circumstances the magnitude of difference between the two is often quite marked (Woodward, 2014). Both RR and OR can be calculated from observational cohort data, however in

case-control studies only the OR may be calculated because the proportions of cases and controls is determined by the sampling method employed (Petrie & Sabin, 2009). Although historically the OR has been more commonly used in case-control methodology, the advent of more widespread use of logistic regression methodology permitting the calculation of the adjusted OR has led to increased reporting of both unadjusted and adjusted OR in other observational studies (Peat, 2002). The specific logistic regression analysis methods through which adjusted odds ratios were derived are discussed below. Adjusted odds ratios have an important role to play in statistical analysis through removal of the effects of confounders where an association between an exposure and an outcome is described, although it should be noted that this method is regarded as the weakest approach statistically when compared with methods such as matching or stratification which require much larger samples sizes (Peat, 2002). Given the importance of adjustment for confounders in the current study and the fact that odds ratios are widely reported in comparable cardiac arrest studies internationally (Arslan Hanif et al., 2010; Studnek et al., 2010; Takei et al., 2010; Egly et al., 2011; Kajino et al., 2011; Nagao et al., 2012; Wang et al., 2012; McMullan et al., 2014), this was felt to be the most appropriate approach which would permit direct comparison with results from other resuscitation populations.

A key consideration associated with observational research is the influence of confounding variables on apparent associations identified through data analysis. Identifying an association is part of the process of eventually establishing causation, although the limitations associated with observational research frequently preclude this. At the outset, it was anticipated that some patients within the study might be exposed to more than one airway management technique. Evidence from previous studies suggests that this might result from procedural complications leading to abandonment of one technique in favour of another or the subsequent arrival of practitioners capable of performing a broader range of advanced airway management techniques during the course of a resuscitation attempt (Wang & Yealy, 2006b). It was therefore established that intention-to-treat analyses might be required to protect against bias in cases of crossover between airway management approaches (Woodward, 2014).

However, the mere presence of an apparent association is insufficient to definitively establish causation where data are observational rather than experimental and insufficient evidence exists to refute other plausible explanations resulting from confounding factors (Woodward, 2014). The use of regression analysis facilitates investigation of the influence of multiple variables on a given dependent variable through determination of the extent to which one or more of the explanatory variables is related to the dependent variable after adjustment for other variables that may relate to

it (Petrie & Sabin, 2009). Conventionally, multiple linear regression is employed, although this requires an adequate sample size (Peat & Barton, 2014). A crucial limitation of linear regression is that it cannot incorporate dependent variables that are dichotomous or categorical and, under these circumstances, logistic regression must be performed (Burns & Burns, 2008). In the current study, the primary outcome variable of interest was neurological outcome either dichotomised as good versus poor or categorised by individual CPC score. In view of this, logistic regression was determined to be the most appropriate approach to multivariate analysis. Logistic regression permits evaluation of the probability that an individual with a particular covariate pattern will have the outcome of interest, in this case good neurological outcome, and thus the risk or odds of the outcome occurring relative to other participants (Petrie & Sabin, 2009). This is particularly relevant in investigating the influence of airway management approach on outcomes. Logistic regression is also most suited to cross-sectional and cohort studies and is therefore an appropriate technique in the context of the longitudinal follow up undertaken as part of the current study (Peat & Barton, 2014).

The blockwise or hierarchical approach to logistic regression has been described as the default technique and is commonly used (Pallant, 2010; Field, 2013). In this method, the order in which predictors are entered into the model is determined by the researcher based on previous research (Field, 2013). Although alternative approaches to logistic regression incorporating stepwise methods exist, these have been criticised for excessive reliance on mathematical criteria resulting in the risk of over-fitting or under-fitting the model and the potential for considerable suppressor effects (Warner, 2013). These methods are prone to influence by random variation in data which can result in the inclusion or removal of variables on purely statistical grounds (Pallant, 2010). This is a concern in cardiac arrest research where established predictors of outcome such as the Utstein criteria (Perkins et al., 2015) exist and are reported internationally. In contrast, the blockwise approach enables the researcher to select predictors based on previous work, thus allowing both known predictors from other studies and those identified as significant in this dataset to be incorporated into the model in a relatively more controlled manner (Field, 2013).

At the outset, it was noted that due to the observational nature of the study, a range of statistical tests would be applied to multiple variables in order to control for confounding and provide further insight in relation to the cumulative effect of multiple variables on outcome. Where more than one comparison is made the potential for type 1 error, where an effect is identified when in reality there is none, is increased (Petrie & Sabin, 2009; Field, 2013). This is referred to as multiple comparison theory, and a number of statistical procedures have been developed to address this issue (Cao &

Zhang, 2014). Although the decision to define a significance level of p<.05 a priori is consistent with statistical convention (Field, 2013), in real terms the impact of this is that there is a five percent chance of making a false-positive inference (Woodward, 2014). In probability terms, when conducting a single test at the five percent level of significance in cases where no effect exists, 95% of the time the test will arrive at the correct conclusion. However, if twenty tests are performed the probability that at least one false-positive result will occur is 64% (Cao & Zhang, 2014). The most straightforward adjustment for multiple testing is the application of the Bonferroni rule, which states that where *m* comparisons are made, the *p* value for each individual test should be multiplied by *m*. In practical terms, if ten tests are conducted, significance should be adjusted to .005 on the basis of the Bonferroni correction (Field, 2013). In view of this, the potential need for application of multiple comparison procedures in the presence of multiple tests was considered as part of pre-planned analyses of results if required.

5.12 Ethical considerations

Ethical approval for the study was granted by the National Research Ethics Service (NRES) Committee (London – Harrow) on 4th February 2013 (Ref: 12/LO/1911) (appendix 5). A further favourable opinion was also subsequently provided by the Health Research Authority Confidentiality Advisory Group (CAG) on the 10th May 2013 (CAG 1-06 PR6/2013) (appendix 6). Approval via CAG was a necessary part of the ethics process in order to gain approval to process clinical data under limited conditions without informed consent.

The study did not require any alterations to the routine clinical care provided by LAS clinicians, which was based on National Clinical Guidelines for use by UK Ambulance Services and Trust specific operating procedures throughout the data collection period. It was therefore not anticipated that any patient would be harmed as a direct result of participation in this study.

However, the study was publicised both internally within the LAS and at relevant national and international conferences during the data collection period. In view of this, the potential for the Hawthorne effect to alter the behaviour of ambulance clinicians and bias study results was a potential concern (Kumar, 2011). It was anticipated that LAS clinicians were likely to be aware of some of the controversies surrounding airway management in UK ambulance services (Woollard & Furber, 2010), and might be concerned that study results would be used to withdraw certain airway management techniques, such as endotracheal intubation. Conversely, when faced with decisions regarding which airway management approach to adopt, some clinicians may have elected to use a potentially less technically demanding intervention, such as supraglottic airway insertion, because of concerns regarding the level of scrutiny applied by the proposed study.

The requirement for informed consent was an important ethical consideration. Patients suffering cardiac arrest will progress rapidly to a state of unconsciousness and are therefore unable to provide informed consent for participation in any form of research (Bartlett, 2005). When ROSC is achieved the level of consciousness exhibited by the patient may range from complete unconsciousness and a continued need for assisted ventilation through various levels of unconsciousness and confusion, to entirely normal neurological function (Edgren, Hedstrand, Kelsey, Sutton-Tyrrell, & Safar, 1994). Therefore, routinely obtaining informed consent was not possible in the initial stages of the study. In addition, the fact that a patient fulfilled the enrolment criteria for this study by definition meant that they had a life threatening medical emergency, and therefore delaying treatment in order to obtain informed consent for study participation would have been impracticable and potentially detrimental (Coats & Goodacre, 2009; Kamarainen, Silfvast, Saarinen, Virta, & Virkkunen, 2012). It was therefore established that the informed consent process or engagement with a consultee where applicable would be undertaken at a later date (Department of Health, 2008). In cases where death occurred prior to discharge, consideration was given to the extent to which consultation with relatives or close friends might provoke unnecessary anxiety or upset in relation to patients where physiological data had already been collected from the prehospital phase (Davies & Collins, 2006). In view of this, support from the Health Research Authority Confidentiality Advisory Group was sought to facilitate retention of data collected in these circumstances without recourse to consultees in accordance with Section 251 of the National Health Service Act 2006 (Health Research Authority, 2014). Collectively, these approaches ensured that the research process did not delay vital medical care, and are consistent with the Declaration of Helsinki and the Mental Capacity Act concerning requirements for informed consent in emergency situations (Lewis, Duber, Biros, & Cone, 2009).

It was anticipated that recalling the events associated with cardiac arrest might be distressing for participants or consultees, and the potential for the development of Post-Traumatic Stress Disorder (PTSD) in patients who had experienced cardiac arrest was acknowledged (Parnia, Spearpoint, & Fenwick, 2007). National Institute for Clinical Excellence (NICE) Guidelines on PTSD recommend watchful waiting for the first four weeks after a traumatic event has occurred as symptoms may resolve during this period. General Practitioners should take responsibility for the initial assessment and coordination of care in those experiencing PTSD, including determining the need for emergency medical or psychiatric assessment (National Institute for Clinical Excellence, 2005). Prior to commencement of the SF-36 questionnaire, study participants were advised that they were free to discontinue the telephone interview at any stage if they experienced distress. In the event that a participant disclosed signs or symptoms consistent with PTSD, it was established that they would be

advised to contact their GP or offered the opportunity for the Chief Investigator to initiate GP referral if required.

Ensuring patient and staff confidentiality was a key consideration in the study protocol. Although the lead researcher required access to patient and LAS staff identifiable information, random generation and subsequent use of anonymity numbers enabled this data to be quickly anonymised (Kalra, Gertz, Singleton, & Inskip, 2006). All data relating to the study was stored on a password protected computer to which only the researcher had access throughout the study period. The lead researcher is an NHS employee and healthcare professional registered with the Health and Care Professions Council, and was therefore bound by the requirements of the employer and registering body to maintain patient confidentiality (Health and Care Professions Council, 2012). External transfer of information was facilitated solely by other NHS Trusts and healthcare professionals with similar responsibilities throughout.

5.13 Challenges in the development and approval of the study methodology

The process of developing and refining the study methodology was necessarily tempered by the need to balance the optimum research approach with the appreciable logistical and financial constraints associated with a lone researcher undertaking largely unfunded work. The preceding literature review chapters demonstrate that prior research addressing out-of-hospital airway management has been conducted in a range of settings internationally using a broad mix of methodologies. These range from single-site retrospective reviews (Egly et al., 2011) to largescale analyses of international cardiac arrest registries with data contributed by multiple EMS services (McMullan et al., 2014). However, there is significant variation in both EMS operating systems (Lockey, 2009) and the legal and ethical frameworks underpinning research between different study settings (Thompson, 2003; Morgans, 2010; Bossaert et al., 2015). It was therefore vital to guard against uncritical importation of individual study methods without due regard for the UK research and clinical practice contexts.

Obtaining ethical approval represented one of the most challenging aspects of the development of the study methodology. In the context of a proposed study involving adult participants who are initially unable to provide consent at the point of contact, the processes for ethical approval are necessarily stringent and comprehensive (Bryman, 2012). Initial feedback from the NHS research ethics committee required a number of refinements to the study procedure in order to satisfy recommendations designed to safeguard privacy and ensure adequate engagement of hospital clinicians in the process. Concerns were raised regarding the overly technical language used in the study participant information materials and restrictions were placed on the number of attempts that

could be made to follow-up survivors. Following satisfactory amendments to the study process and associated materials, it was necessary seek approval from the Confidentiality Advisory Group in order to process data without consent for research purposes under the terms of The Health Service (Control of Patient Information) Regulations 2002. Although this was ultimately granted, the application could not proceed until ethics committee approval had been obtained, leading to appreciable delays in the commencement of data collection.

A number of challenges associated with conducting out-of-hospital airway management and cardiac arrest research were also identified during the study methodology development and ethical approval phases of the research programme. Unlike randomized or interventional trials (Petrie & Sabin, 2009), the current study required no alteration to standard ambulance service management of cardiac arrest. However, although the host EMS system has a well-established pre-existing cardiac arrest registry (Fothergill et al., 2013), data collection procedures for the current study required additions to standard notification mechanisms in order to alert the researcher to cases fulfilling inclusion criteria. In common with a number of UK ambulance services, clinical records within the host service are exclusively paper-based, with the caveat that computer-aided dispatch systems generate electronic data primarily related to triage codes and call information rather than details of clinical interventions and patient demographics. Each case of cardiac arrest included in the study would be expected to generate paper-based records relating to ECG, vital signs and capnography monitoring in addition to written patient report forms completed by ambulance clinicians attending the scene, which are then scanned into an electronic database. In keeping with other UK prehospital research, this results in delays in accessing records and increases the potential for data loss (Pocock et al., 2016). In contrast with the hospital setting where patients are usually identifiable and clinical records available, out-of-hospital resuscitation may involve patients in whom demographic and clinical information are not readily available. Identification and tracking of the in-hospital course for patients with the potential for admission to several HAC sites in cases where the prehospital record is incomplete is therefore particularly challenging and requires close cooperation and coordination between the researcher, host EMS system and HACs as identified in previous studies (Lyon, Egan, et al., 2010). An inevitable consequence of these challenges is that some patients will be lost to follow-up, as seen in previous studies addressing long-term neurological outcomes in patients undergoing advanced airway management by paramedics (Bernard, Nguyen, et al., 2010).

5.14 Summary

This chapter has outlined the process of developing and refining the study methodology, informed by comprehensive review of previous airway management studies and a sound understanding of factors known to influence outcome in out-of-hospital cardiac arrest. The final methodological approach represents the culmination of extensive critical appraisal of existing studies, stepwise establishment of a dataset sufficient to address the research question, and evaluation of time and resource constraints. The next section presents the results of the data collection and analysis processes, which ultimately represent the products of the methodological approach.

6. Results

6.1 Introduction

This chapter describes the raw data and provides details of the results of statistical analysis. Monthly recruitment numbers and associated exclusions are detailed and the characteristics of the final study sample and cases lost to follow-up are described. Results and associated statistical analysis are reported in a stepwise fashion, progressing from participant demographics, key prehospital timings, ECG findings and ambulance service and initial hospital treatment, to bivariate and multivariate analysis stratified by airway management approach. In the final section, a range of binomial logistic regression models and associated odds ratios are presented alongside results from administration of the SF36 health survey.

6.2 Study sample

A total of 220 patients were recruited into the study, with complete outcome data obtained for 95% (n=209). Numbers recruited by month with associated exclusions are shown below (Figure 3). In all excluded cases a prehospital physician performed advanced airway management utilising rapid sequence induction (RSI) of anaesthesia. These cases were excluded on the basis that RSI is not routinely available to paramedics (Woollard & Furber, 2010) and is therefore not representative of standard ambulance service scope of practice. The use of RSI post ROSC has also been shown to predict improved survival (Kwok, Prekker, Grabinsky, Carlbom, & Rea, 2013) and therefore represents a source of bias and potential confounding (Peat, 2002)

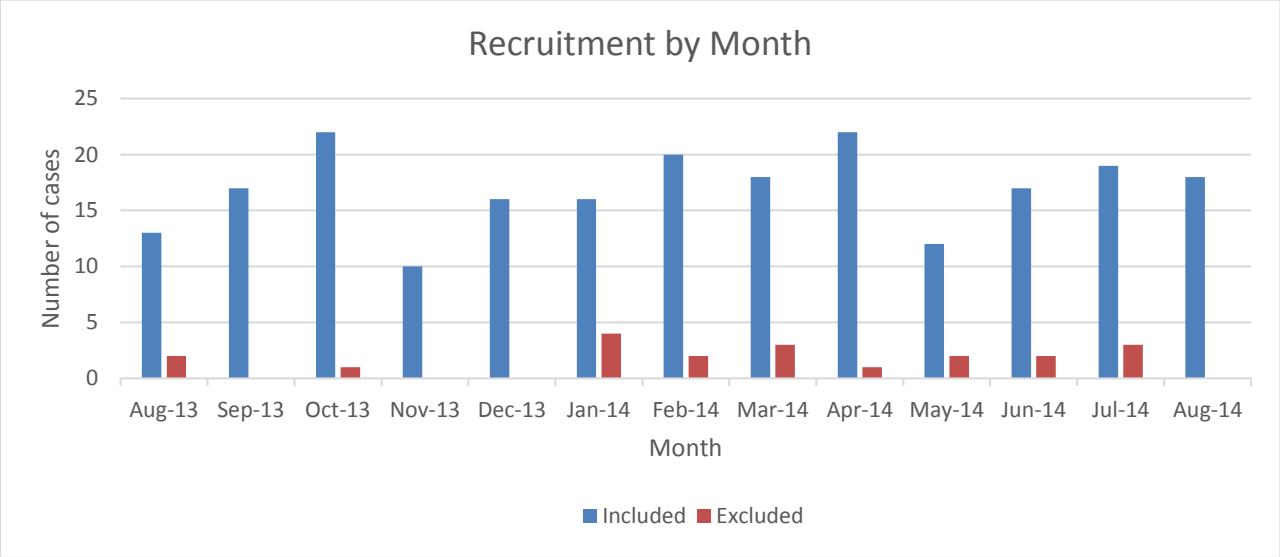

Figure 3 Recruitment by month

Of the 11 patients without complete outcome data, 4 (36.5%) were transferred to other Intensive Care Unit (ICU) facilities and therefore no assessment of their neurological outcome at discharge

could be undertaken. In the remaining cases, sufficient clinical data to facilitate calculation of Cerebral Performance Category could not be retrieved and these patients were also excluded from further analysis. The mean age of patients lost to follow-up was 68.1 years (range 40-97 years) and 63.6% (n=7) were male. Further clinical characteristics of these patients are shown below (Tables 6.1.1 and 6.1.2). Of the 209 cases included in the final analysis for whom complete outcome data were available, mean age was 66.8 years (range 22-96 years) and 67.7% (n=149) were male. Mean age for male patients (65.8 years, range 22-91, SD 12.7) was marginally lower than that of female patients (69.2 years, range 37-96, SD 13.8). Clinical and demographic characteristics for the 209 cases included in final analysis are shown below. Chi-square and Mann-Witney U test analyses demonstrated no significant variation in key clinical characteristics between patients lost to follow-up and those included in the final analysis (Tables 10 and 11).

Table 10 Clinical and demographic characteristics of patients included in final analysis and those lost to follow-up (excluded)

Characteristic	**Included Cases**	**Excluded Cases**	**Chi Square**	**DF**	**P value***
Male	149 (71.3%)	7 (63.6%)	0.042	1	.838
Female	60 (28.7%)	4 (36.4%)			
Shockable Rhythm	135 (64.6%)	8 (72.7%)	0.052	1	.820
Non-shockable Rhythm	74 (35.4%)	3 (27.3%)			
Witnessed Arrest	172 (82.3%)	9 (81.8%)	0.000	1	1.00
Unwitnessed Arrest	37 (17.7%)	2 (18.2%)			
Bystander CPR	125 (59.8%)	9 (81.8%)	1.302	1	.254
No Bystander CPR	84 (40.2%)	2 (18.2%)			
Endotracheal Intubation	57 (27.3%)	3 (27.3%)	0.000	1	1.00
Supraglottic Airway	152 (72.7%)	8 (72.7%)			
Presenting ECG – Asystole	38 (18.2%)	2 (18.2%)	0.517	2	.772
Presenting ECG – PEA	36 (17.2%)	1 (9.1%)			
Presenting ECG – VF	135 (64.6%)	8 (72.7%)			

*Continuity correction reported where expected frequencies <5

Table 11 Median age of patients included in final analysis and those lost to follow-up (excluded)

Characteristic	**Included Cases (median)**	**Excluded Cases (median)**	**U***	**z**	**p value**
Age	67 (22-96)	69 (40-97)	1086.5	-.306	.759

*Mann-Whitney test

The following results are derived from the 209 patients for whom complete outcome data were available. Distribution of age stratified by gender for these patients is shown below (Figure 4). The peak in volume of cases for female patients occurred in older age groups when compared with male patients.

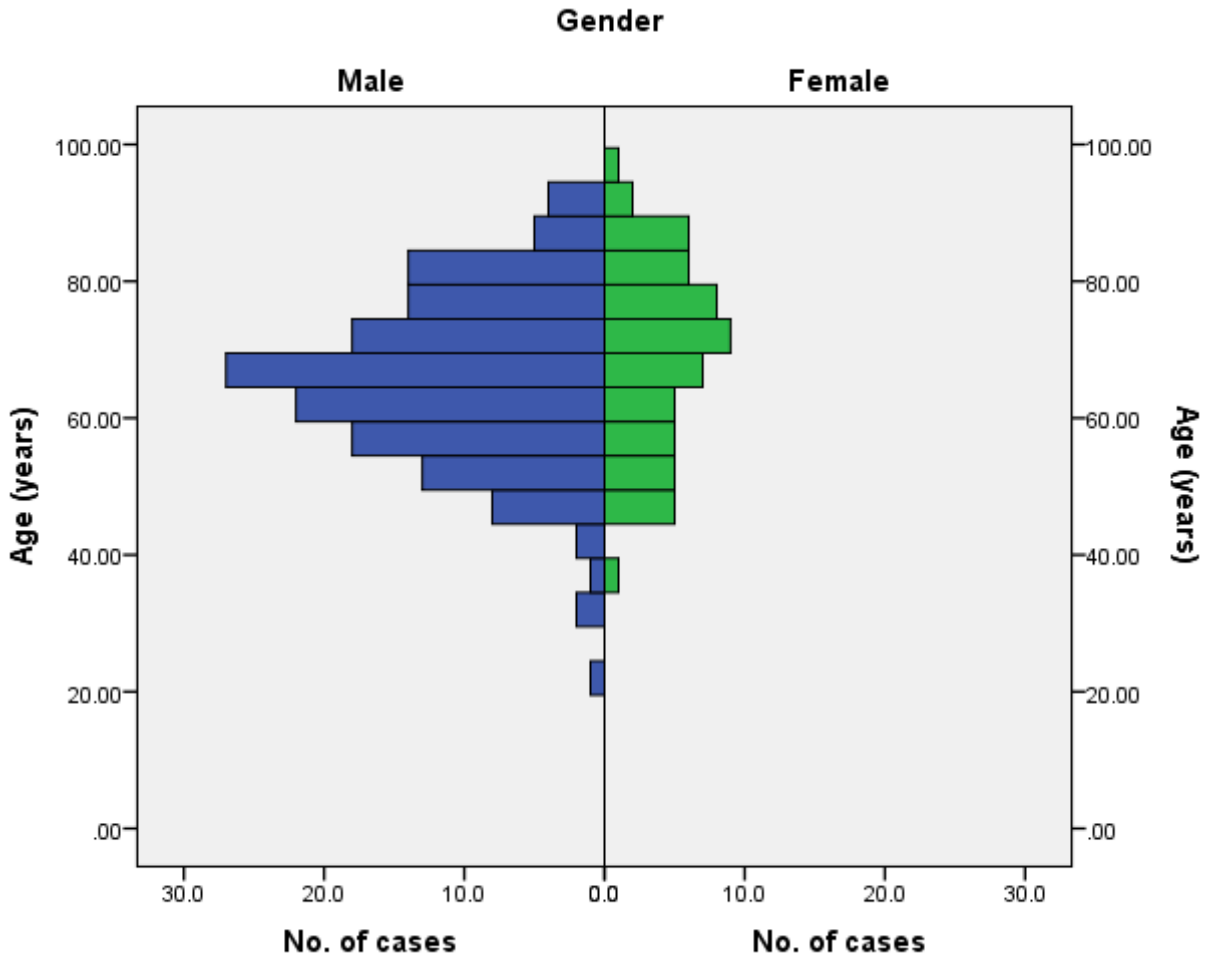

Figure 4 Age range of participants stratified by gender

6.3 Key timings

Key timings for response, clinical interventions and subsequent transfer to definitive care are shown below (Table 12). Patients were most frequently attended within 6 minutes of the 999 call, which is within the 8-minute response time target that UK ambulance services are required to meet for patients in cardiac arrest (Durham, Faulkner, & Deakin, 2016). Resuscitation was most commonly commenced by attending ambulance staff one minute after arrival at the scene. Mean time from arrival to commencement of transfer to the HAC was less than an hour with a median transfer time of 14 minutes (range 1-49 minutes).

Table 12 Key timings for response, clinical interventions, and transfer to definitive care

Timing (mins)	Mean (SD)	Median (Range)	Mode
Call to arrival of first resource	6.5 (4.1)	6.0 (1-48)	6.0
Arrival of first resource to CPR	3.1 (4.0)	2.0 (0-32)	1.0
Arrival of first resource to advanced airway placement	12.2 (7.3)	10.0 (1-43)	10.0
Arrival of first resource to ROSC	26.6 (14.8)	24.0 (5-87)	27.0
Arrival of first resource to departure to HAC	56.3 (19.5)	54.0 (7-143)	44.0
Transfer time to HAC	16.27 (8.7)	14.0 (1-49)	11.0

The distribution of arrival of first resource to commencement of CPR times stratified by whether the cardiac arrest was witnessed or not is show below (Figure 5). There were no cases in the unwitnessed cardiac arrest group where the arrival to CPR time exceeded 8 minutes. Multiple factors such as obtaining access to a property or locating an address can affect time of arrival to CPR interval, however it was not possible to determine these from the clinical records. All cases exceeding 8 minutes in the witnessed arrest group were in patients where the arrest occurred in the presence of the ambulance clinicians during treatment at scene.

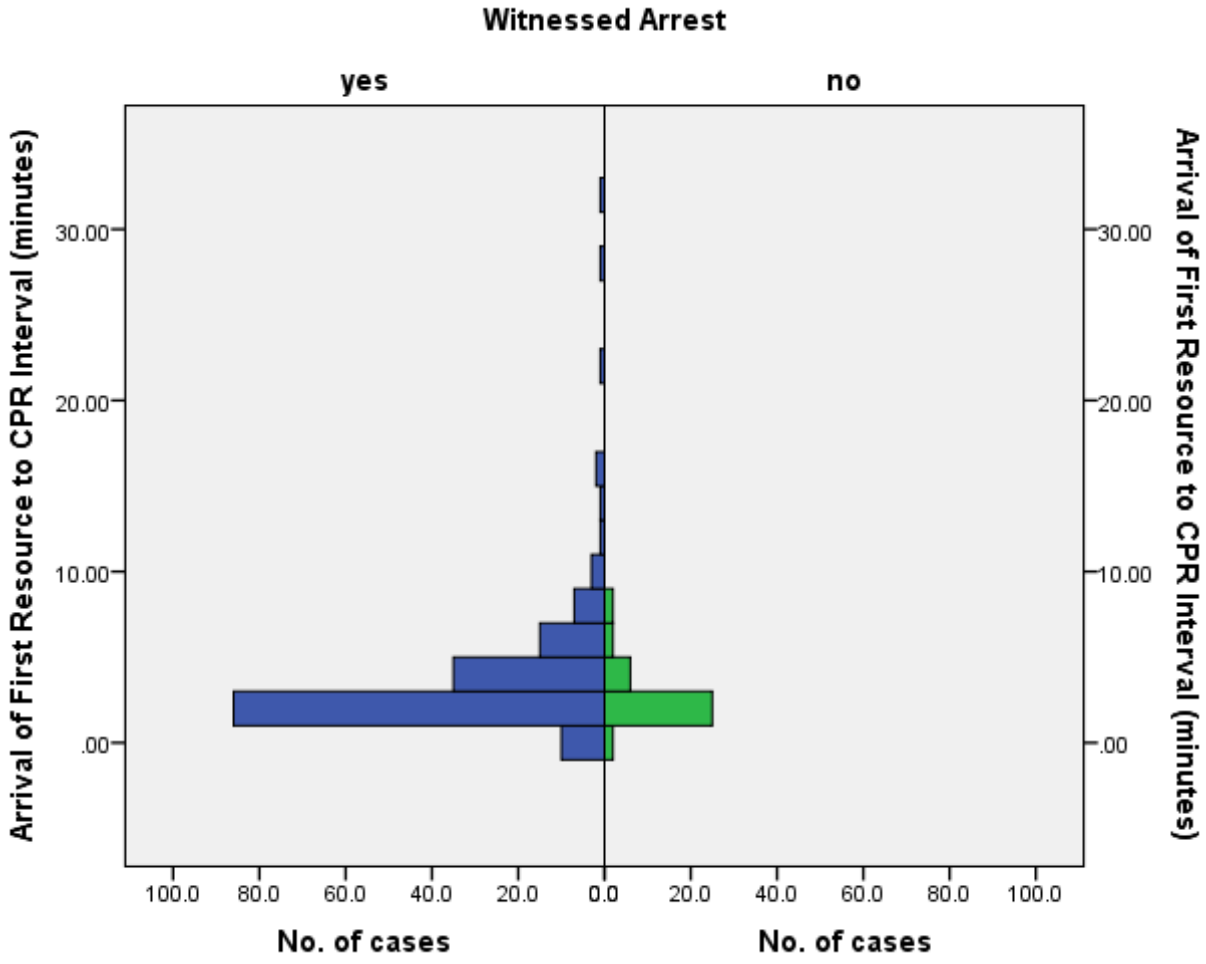

Figure 5 Arrival of first resource to CPR time stratified by whether the arrest was witnessed or not

6.4 Presenting ECG

Almost two thirds of patients (64.6%) presented in a shockable rhythm (Table 13). In 82.3% (n=172) of cases the cardiac arrest was witnessed and 59.8% (n=125) of patients received bystander CPR.

Table 13 Presenting ECG

Rhythm	**Number of Cases**
Ventricular Fibrillation	135 (64.6%)
Pulseless Electrical Activity	36 (17.2%)
Asystole	38 (18.2%)

A proportion of patients who initially presented in a non-shockable rhythm subsequently received one or more shocks suggesting that the ECG converted to a shockable rhythm during resuscitation attempts (n=74, 35.4%). There was no difference in the proportion of patients who converted to a shockable rhythm between the PEA and asystole groups (Table 14).

Table 14 Proportions of patients presenting in asystole and PEA converting to a shockable rhythm during resuscitation

		Asystole	**PEA**	**Chi-Square**	**DF**	**p value**
Converted to shockable	Yes	11 (50%)	11 (50%)	0.000	1	1.00
	No	27 (51.9%)	25 (48.1%)			

6.5 Prehospital 12 lead ECG Diagnosis

Overall, ST segment elevation was present in 84.1% (n=176) of cases, with anterior STEMI constituting the most common (45.9%, n= 96) and posterior STEMI (3.3%, n=7) the least common diagnoses (Table 15). In one case the prehospital ECG diagnosis was not recorded. Almost one in ten patients (9.6%, n=20) were transferred with an ECG diagnosis of ST depression which is not within the criteria for activation of the HAC pathway within the host EMS service.

Table 15 Prehospital 12 lead ECG diagnosis

12 Lead ECG Diagnosis	**Number of cases**
Anterior ST Elevation	96 (45.9%)
Inferior ST Elevation	63 (30.1%)
Lateral ST Elevation	10 (4.8%)
Posterior ST Elevation	7 (3.3%)
ST Depression	20 (9.6%)
Left Bundle Branch Block	12 (5.7%)

Although there was no significant variation in the ECG characteristics of patients presenting in a shockable rhythm or undergoing angiography, those identified as having ST depression on the post ROSC ECG were less likely to undergo angiography than those with ST elevation or left bundle branch block. A higher proportion of patients with post ROSC ST elevation or Left Bundle Branch Block presented in a shockable rhythm compared with those diagnosed with ST depression alone (Table 16).

Table 16 ECG characteristics of patients presenting in a shockable rhythm and undergoing angiography

		ST Elevation	ST Depression	LBBB	Chi-Square	DF	p value
Angiography performed*	Yes	129 (73.7%)	12 (63.2%)	9 (75%)	0.996	2	.608
	No	46 (26.3%)	7 (36.8%)	3 (25%)			
Shockable**	Yes	116 (65.9%)	10 (50%)	9 (75%)	2.565	2	.277
	No	60 (34.1%)	10 (50%)	3 (25%)			

*n= 3 cases missing (n= 2 cases without ECG diagnosis, n=1 case with angiography unknown)

**n=1 case missing (ECG diagnosis unknown)

6.6 Prehospital data

The final airway management approach in the majority of patients was supraglottic airway (72.7%, n=152) with the remainder undergoing endotracheal intubation (27.3%, n=57). In 22 (10.5%) of these patients, a combination of airway management techniques was used. In six cases a supraglottic airway was inserted following a failed ETI attempt. In the remaining sixteen cases a supraglottic airway was removed and successful ETI performed. No patients were managed via basic measures alone. Data analyses were predominantly conducted based on the final airway approach, supplemented by a further intention-to-treat analysis categorising patients according to the first airway management technique to which they were exposed.

6.7 Physiological resuscitation data

Vital signs obtained during CPR or immediately post ROSC are shown below (Table 17). The majority of patients were normothermic (median 35.6^{o}C, range 12.2-37.7^{o}C) with modal blood glucose measurement within normal parameters (7.2 mmol/l). Post ROSC mean heart rate (95/min, SD 30.8), systolic blood pressure (131 mmHg, SD 30.0) and $ETCO_2$ (4.7 kPa, SD 2.08) were within normal limits.

Table 17 Physiological resuscitation data

Physiological Measurement	Mean (SD)	Median (Range)	Mode
Tympanic Temperature ^{O}C	35.2 (2.3)	35.6 (12.2-37.7)	36
Blood Capillary Glucose (mmol/l)	9.6 (4.2)	8.8 (1.9-27.7)	7.2
First recorded post ROSC heart rate (beats per minute)	95 (30.8)	94 (0-222)	100
First recorded post ROSC systolic blood pressure (mmHg)	131 (30.0)	130 (56-210)	128
First recorded End tidal CO_2 (kPa)	4.7 (2.08)	4.2 (0.9-13.3)	2.9

6.8 Prehospital management

Data for prehospital therapeutic interventions are shown below (Table 18). A median of three shocks were delivered to patients, with a single shock constituting the modal value. The median 250 ml (range 0-2000) of intravenous fluids provided to patients is consistent with the post ROSC treatment algorithm employed by the host EMS service, which recommends an initial 250 ml bolus in hypotensive patients prior to initiation of inotropic support.

Table 18 Prehospital therapeutic interventions

Clinical Interventions	Mean (SD)	Median (Range)	Mode
Total Number of Shocks (VF/VT only n=135)	3.7 (3.3)	3 (0-20)	1
Total volume of fluid (ml)	254 (306.7)	250 (0-2000)	0
Total intra-arrest adrenaline (mg)	2.68 (2.6)	2 (0-12)	0
Total post ROSC adrenaline (mg)	0.467 (0.1)	0 (0-0.9)	0

The proportion of patients administered atropine stratified according to ambulance 12 lead ECG diagnoses varied from no administration in cases of lateral and posterior STEMI and Left Bundle Branch Block to 17.5% (n=11) of cases in the presence of inferior STEMI (Table 19). This variation was not statistically significant (χ^2 (5, N=208) = 9.157, p=.103).

Table 19 Administration of post ROSC atropine stratified by ECG diagnosis

12 lead ECG Diagnosis	Post ROSC Atropine	
	Yes	No
Anterior	6 (6.3%)	90 (93.8%)
Lateral	0 (0%)	10 (100%)
Inferior	11 (17.5%)	52 (82.5%)
Posterior	0 (0%)	7 (100%)
LBBB	0 (0 %)	12 (100%)
ST Depression	2 (10%)	18 (90%)

Post ROSC adrenaline was used more frequently than atropine, and administered to a proportion of patients in all categories of prehospital 12 lead ECG diagnoses, ranging from 15.6% (n=15) of patients diagnosed with anterior STEMI to 40% (n=4) of patients diagnosed with lateral STEMI (Table 20). This variation was not statistically significant (χ^2 (5, N=208) =7.164, p=.209).

Table 20 Administration of post ROSC adrenaline stratified by ECG diagnosis

12 lead ECG Diagnosis	**Post ROSC Adrenaline**	
	Yes	**No**
Anterior	15 (15.6%)	81 (84.4%)
Lateral	4 (40.0%)	6 (60.0%)
Inferior	19 (30.2%)	44 (69.8%)
Posterior	1 (14.3%)	6 (85.7%)
LBBB	2 (16.7%)	10 (83.3%)
ST Depression	4 (20.0%)	16 (80.0%)

6.9 Clinical and demographic variables associated with administration of intra-arrest adrenaline

Adrenaline was given intra-arrest as part of clinical management in 161 cases. Median time to ROSC was significantly longer in patients administered adrenaline (30.2 mins versus 14.5 mins, p<.001) and a lower proportion of patients presenting in a shockable rhythm were administered adrenaline (68.9%, n=93) compared with those in a non-shockable rhythm (91.9%, n=68, p<.001) (Tables 21 and 22).

Table 21 Demographics and clinical characteristics of patients administered intra-arrest adrenaline

		Adrenaline intra-arrest	**Chi-Square**	**DF**	**p value***
Gender	Male	114 (76.5%)	0.010	1	.919
	Female	47 (78.3%)			
Airway	ETI	45 (78.9%)	0.048	1	.827
	SGA	116 (76.3%)			
Witnessed arrest	Yes	131 (76.2%)	0.185	1	.667
	No	30 (81.1%)			
Bystander CPR	Yes	95 (76.0%)	0.071	1	.791
	No	66 (78.6%)			
Shockable	Yes	93 (68.9%)	13.025	1	<.001
	No	68(91.9%)			
Angiography**	Yes	112 (74.2%)	1.670	1	.196
	No	47 (83.9%)			
CPC	Good	28 (47.5%)	38.349	1	<.001
	Poor	133 (88.7%)			

*Continuity correction reported where expected frequencies <5

**In two cases, it could not be determined whether the patient had undergone angiography

Table 22 Age and key timings for patients administered intra-arrest adrenaline

Median	**Intra-arrest adrenaline**		**U***	**z**	**p value**
	Yes	**No**			
Call to arrival (mins)	6.7 (1-48)	6.0 (1-13)	3593.5	-0.741	.458
Age (years)	67.0 (22-96)	65.6 (34-91)	3574.5	-0.787	.431
Time to ROSC (mins)	30.2 (9-87)	14.5 (5-59)	859.5	-8.132	<.001

*Mann Whitney test

Significantly higher proportions of patients administered intra-arrest adrenaline exhibited poor neurological outcomes (CPC 3-5), with data patterns demonstrating increasing proportions of patients categorised as CPC3 and above in the adrenaline group (Table 23).

Table 23 Cerebral Performance Category outcome for patients administered adrenaline

		CPC1	CPC2	CPC3	CPC4	CPC5
Intra-arrest adrenaline	Yes	17 (39.5%)	11(68.8%)	11 (73.3%)	6 (85.7%)	1 (90.6%)
	No	26 (60.5%)	5 (31.2%)	4 (26.7 %)	1 (14.3%)	12 (9.4%)

(χ^2 (4, N=209) =48.576, p<.001)

6.10 Clinical and demographic variables stratified by airway management approach

Variation in clinical characteristics and patient demographics have the potential to bias outcomes regardless of airway management approach. However, there was no significant variation in clinical and demographic variables stratified by airway management approach (Tables 24 and 25). Median number of shocks delivered and doses of intra-arrest and post ROSC adrenaline were the same in both airway management groups. These findings are important in addressing confounding factors and providing the underpinning data required for more sophisticated statistical analysis including binomial logistic regression modelling of neurological outcomes.

Table 24 Demographics and clinical characteristics stratified by airway management approach - dichotomous variables

		ETT (n=57)	SGA (n=152)	Chi-Square	DF	p value*
Gender	Male	42 (73.7%)	107 (70.4%)	0.088	1	.767
	Female	15 (26.3%)	45 (29.6%)			
Witnessed Arrest	Yes	44 (77.2%)	128 (84.2%)	0.961	1	.327
	No	13 (22.8%)	24 (15.8%)			
Bystander CPR	Yes	35 (61.4%)	90 (59.2%)	0.017	1	.897
	No	22 (38.6%)	62 (40.8%)			
Shockable Rhythm	Yes	33 (57.9%)	102 (67.1%)	1.161	1	.281
	No	24 (42.1%)	50 (32.9%)			
Advanced Paramedic	Yes	6 (10.5%)	12 (7.9%)	0.365	1	.546
	No	51 (89.5%)	140 (92.1%)			
Angiography Performed **	Yes	38 (66.7%)	113 (75.3%)	0.107	1	.744
	No	19 (33.3%)	37 (24.7%)			

*Continuity correction reported where expected frequencies <5

**n=2 cases missing

Table 25 Prehospital therapeutic interventions stratified by airway management approach

Median	ETT	SGA	U*	z	p value
Total Number of Shocks (VF/VT only n=135)	3 (1-13)	3 (0-20)	1629.5	-.278	.781
Total volume of fluid (ml)	250 (0-1500)	200 (0-2000)	4049.5	-.373	.709
Total post ROSC adrenaline (mg)	0 (0-0.4)	0 (0-0.9)	4593.5	.919	.358
Total adrenaline intra-arrest (mg)	2 (0-9)	2 (0-12)	3964.0	-.958	.338

*Mann-Whitney test

6.11 Key timings and physiological data stratified by airway management approach

Similarly, there were no significant differences in key timings stratified by airway management approach. Median time to placement of an advanced airway was marginally higher in patients undergoing intubation (11 mins versus 10 mins), although this was not statistically significant. Physiological data were also broadly comparable between the ETT and SGA groups (Table 26).

Table 26 Key timings and physiological data stratified by airway management approach

Median	**ETT**	**SGA**	**U***	**z**	**p value**
Age (years)	68 (22-96)	66 (34-93)	3931.0	-1.030	.303
Arrival of first resource to airway placement (minutes)	11 (1-43)	10 (1-33)	13869.5	-1.463	.144
Call to arrival of first resource (minutes)	6 (2-17)	6 (1-48)	4757.5	1.101	.271
Arrival of first resource to CPR (minutes)	2 (0-9)	2 (0-32)	4020.0	.353	.724
Arrival of first resource to ROSC (minutes)	25 (5-79)	24 (6-87)	3840.0	-.894	.372
Arrival of first resource to departure to HAC (minutes)	54 (31-92)	55 (7-143)	4131.5	-.515	.607
Transfer time to HAC (minutes)	14 (4-43)	14 (1-49)	4362.5	.078	.937
Tympanic temperature (^{o}C)	35.6 (34.1-37)	35.6 (12.2-37.7)	1935.0	-.114	.909
Blood capillary glucose (mmol/l)	9 (3.8-27.7)	8.8 (1.9-27.7)	3796.0	-.473	.636
First recorded post ROSC heart rate (beats per minute)	90 (7-150)	96 (0-222)	4777.0	1.304	.192
First recorded post ROSC systolic blood pressure (mmHg)	128 (75-203)	130 (56-210)	4184.0	-.380	.704
First recorded End tidal CO2 (kPa)	4.1 (1.3-9.5)	4.3 (0.9-13.3)	1415.0	-.221	.825

*Mann-Whitney test

6.12 Factors associated with good versus poor outcome

A higher proportion of patients presented in a shockable rhythm in the good versus poor outcome group (91.5%, n=54 versus 54%, n=81, p<.001). Significantly higher proportions of patients with a good outcome underwent angiography (91.5%, n=54 versus 65.5%, n=97, p<.001). Conversely, higher proportions patients in the poor outcome group experienced an episode of hypotension (11.3%, n=17 versus 0.0%, n=0, p<.001) and were administered post ROSC adrenaline (30.0%, n=45 versus 1.7%, n=1, p<.001), which is indicated in the host EMS system for the management of hypotension refractory to treatment with intravenous fluids. The proportions of patients suffering a witnessed arrest and exposed to bystander CPR did not differ significantly between outcome groups (Table 27).

Table 27 Factors associated with good versus poor outcome - dichotomous variables

		Good Outcome (CPC 1&2) %	Poor Outcome (CPC 3-5) %	Chi-Square	DF	p value*
Gender	Male	47 (79.7%)	102 (68.0%)	2.272	1	.132
	Female	12 (20.3%)	48 (32.0%)			
Witnessed Arrest	Yes	49 (83.1%)	123 (82.0%)	0.000	1	1.00
	No	10 (16.9%)	27 (18.0%)			
Bystander CPR	Yes	41 (69.5%)	84 (56.0%)	2.670	1	.102
	No	18 (30.5%)	66 (44.0%)			
Shockable Rhythm	Yes	54 (91.5%)	81 (54.0%)	24.457	1	<.001
	No	5 (8.5%)	69 (46.0%)			
Advanced Paramedic	Yes	5 (8.5%)	13 (8.7%)	0.000	1	1.00
	No	54 (91.5%)	137 (91.3%)			
Angiography Performed	Yes	54 (91.5%)	97 (65.5%)	13.146	1	<.001
	No	5 (8.5%)	51 (34.5%)			
Any SBP < 90mmHg	Yes	0 (0%)	17 (11.3%)	5.841	1	.016
	No	59 (100%)	133 (88.7%)			
Post ROSC Adrenaline	Yes	1 (1.7%)	45 (30.0%)	18.149	1	<.001
	No	58 (98.3%)	105 (70.0%)			

*Continuity correction reported where expected frequencies <5

Further stratification of neurological outcome by presenting rhythm demonstrated that outcomes for patients presenting in PEA or asystole were generally poor, whereas higher proportions of patients presenting in a shockable rhythm achieved good clinical outcomes (Table 28).

Table 28 Good versus poor outcome stratified by presenting rhythm

	Good Outcome (CPC 1&2) %	Poor Outcome (CPC 3-5) %	Chi-Square	DF	p value
Asystole	3 (5.1%)	35 (23.3%)	26.122	2	<.001
PEA	2 (3.4%)	34 (22.7%)			
Shockable	54 (91.5%)	81 (54%)			

A higher proportion of patients who subsequently developed a shockable rhythm after initially presenting in PEA or asystole survived with good neurological outcome, although this was not significant when outcome was dichotomised as good versus poor (Table 29) or stratified by individual CPC category (Table 30).

Table 29 Outcomes for patients converting to a shockable rhythm

		Good Outcome (CPC 1&2) %	Poor Outcome (CPC 3-5) %	Chi-Square	DF	p value
Converted to shockable	Yes	3 (13.6%)	19 (86.4%)	1.055	1	.304
	No	2 (3.8%)	50 (96.2%)			

Table 30 Cerebral Performance Category for patients converting to a shockable rhythm

		CPC 1	CPC 2	CPC 3	CPC 4	CPC 5
Converted to shockable	Yes	2 (9.1%)	1 (4.5%)	0 (0%)	0 (0%)	19 (86.4%)
	No	1 (1.9%)	1 (1.9%)	1 (1.9%)	1 (1.9%)	48 (92.3%)

X^2 (4, N=74) =3.259, p=.515

Analysis of age and timings and physiological data between outcome groups are shown below (Table 31). Median age was significantly lower in patients with good neurological outcome (61 years versus 69 years, p<.001). Median time from arrival of first resource to ROSC (16 mins versus 27 mins, p<.001) and departure to HAC (45 mins versus 57 mins, p<.001) were also significantly lower in the good outcome group. Median response and HAC transfer times and intervals to starting CPR and placing an advanced airway did not vary significantly. There was no significant variation in physiological measurements between the two groups, with the exception of a lower median $ETCO_2$ observed in the good outcome group (4.4 kPa versus 4.8 kPa, p=.042) although this is unlikely to be clinically significant.

Table 31 Factors associated with good versus poor outcome

	Good outcome (CPC 1&2)	Poor outcome (CPC 3-5)	U*	z	p value
Age (years)	61 (22-85)	69 (34-96)	6090.0	4.232	<.001
Arrival of first resource to airway placement (minutes)	10 (2-41)	11 (1-43)	4360.0	.735	.462
Call to arrival of first resource (minutes)	6 (1-13)	6 (1-48)	4473.5	.124	.901
Arrival of first resource to CPR (minutes)	2 (0-28)	2 (0-32)	4303.0	.631	.528
Arrival of first resource to ROSC (minutes)	16 (5-48)	27 (6-87)	6516.5	5.53	<.001
Arrival of first resource to departure to HAC (minutes)	45 (7-95)	57 (17-143)	6344.0	4.878	<.001
Transfer time to HAC (minutes)	14 (1-49)	14 (2-40)	4025.0	-1.018	.309
Tympanic temperature (^oC)	35.5 (12.2-37)	35.6 (30-37.7)	2245.0	.770	.441
Blood capillary glucose (mmol/l)	8.6 (1.9-27.7)	8.9 (3.3-24.6)	4545.0	1.187	.235
Highest ETCO2 (kPa)	4.4 (2.7-9)	4.8 (1.3-13.3)	4649.0	2.033	.042
First Recorded SBP	134 (91-209)	128 (56-210)	3945.5	-1.219	.223

*Mann-Whitney test

6.13 Outcome analysis by Cerebral Performance Category

Repetition of the above analysis stratified by individual CPC category demonstrated similar patterns to those observed in bivariate analysis of good versus poor outcome (Table 32).

Table 32 Median age, prehospital timings and therapeutic interventions stratified by individual CPC category

	CPC1	**CPC2**	**CPC3**	**CPC4**	**CPC5**
Count	43	16	15	7	128
Age (years)	61 (22-76)	63 (37-85)	63 (47-85)	77 (49-48)	70.5 (34-96)
Arrival of first resource to airway placement (minutes)	9 (2-41)	11 (6-25)	9 (5-21)	6 (5-18)	11 (1-43)
Call to arrival of first resource (minutes)	6 (1-13)	5 (1-9)	6 (2-10)	6 (3-19)	6 (1-48)
Arrival of first resource to CPR (minutes)	2 (0-28)	1 (0-5)	2 (1-6)	4 (1-11)	2 (0-32)
Arrival of first resource to ROSC (minutes)	15 (5-34)	18.5 (9-48)	16 (7-48)	38 (15-52)	27 (6-87)
Arrival of first resource to departure to HAC (minutes)	45 (7-95)	44.5 (24-66)	44 (35-60)	59 (39-78)	59 (17-143)
Transfer time to HAC (minutes)	20 (1-49)	13.5 (4-37)	9 (4-30)	16 (4-31)	14.5 (2-40)
Tympanic temperature (^{o}C)	35.5 (31.7-37)	35.15 (12.2-36.6)	36 (34.1-36.8)	34.9 (32.8-37.7)	35.6 (30.0-37.7)
Blood capillary glucose (mmol/l)	8.8 (3.3-27.7)	8.3 (1.9-13.6)	7.6 (3.8-12.10)	9.8 (6.8-13.7)	9.15 (3.3-24.6)
Highest ETCO2 (kPa)	4.7 (2.9-8.7)	4.4 (2.7-9.0)	4.5 (2.8-8.5)	4.2 (2.5-5.2)	5.5 (1.3-13.3)

In terms of statistical significance, median age, time to ROSC and duration of resuscitation at scene prior to HAC transfer were all significantly lower (p<.001) in patients categorised as CPC1 (Table 33). However, median age was the same in the CPC2 and CPC3 groups (63 years) whereas median time to ROSC was marginally higher in CPC2 (18.5 minutes) versus CPC3 (16 minutes) patients. Variation in $ETCO_2$ was significant (p=.047), with the highest median value observed in the CPC5 group. The CPC5 group also demonstrated the greatest variation in $ETCO_2$ values (1.3-13.3 kPa).

Table 33 Factors associated with neurological outcomes

	H*	**DF**	**P value**
Age (years)	25.647	4	<.001
Arrival of first resource to airway placement (minutes)	6.944	4	.139
Call to arrival of first resource (minutes)	2.608	4	.625
Arrival of first resource to CPR (minutes)	6.434	4	.169
Arrival of first resource to ROSC (minutes)	40.192	4	<.001
Arrival of first resource to departure to HAC (minutes)	37.945	4	<.001
Transfer time to HAC (minutes)	5.698	4	.223
Tympanic temperature (^oC)	1.61	4	.807
Blood capillary glucose (mmol/l)	5.162	4	.271
Highest $ETCO_2$	9.616	4	.047

*Kruskal-Wallis test

6.14 Clinical characteristics and demographics of patients undergoing angiography

Clinical characteristics of patients undergoing angiography are shown below (Tables 34 and 35). A significantly higher proportion of male versus female patients were exposed to angiography (81.6%, n=120, versus 51.7%, n=31, p<.001). Patients who underwent angiography were also significantly younger (median 64 years versus 78 years, p<.001) and more likely to have presented in a shockable versus non-shockable rhythm (86.7%, n=117 versus 47.2%, n=34, p<.001). Higher proportions of patients undergoing angiography were also treated with mild therapeutic hypothermia (91.8%, n=89 versus 52.5%, n=52, p<.001). Previous medical history could not be determined in a number of cases, however there was no significant difference in the proportions of patients with specific comorbidities who underwent angiography versus those not exposed to the procedure.

Table 34 Demographic and clinical characteristics of patients undergoing angiography - dichotomous variables

		Angiography Performed (n=207)**		**Missing Cases**	**Chi-Square**	**DF**	**p value***
		Yes	**No**				
Gender	Male	120 (81.6%)	27 (18.4%)	0	17.899	1	<.001
	Female	31 (51.7%)	29 (48.3%)				
Witnessed Arrest	Yes	129 (75.4%)	42 (24.6%)	0	2.410	1	.121
	No	22 (61.1%)	14 (38.9%)				
Bystander CPR	Yes	95 (76%)	30 (24%)	0	1.126	1	.289
	No	56 (68.3%)	26 (31.7%)				
Shockable	Yes	117 (86.7%)	18 (13.3%)	0	35.049	1	<.001
	No	34 (47.2%)	38 (52.8%)				
Systolic BP <90 mmHg	Yes	9 (52.9%)	8 (47.1%)	0	2.733	1	.098
	No	142 (74.7%)	48 (25.3%)				
Therapeutic Hypothermia	Yes	89 (91.8%)	8 (8.2%)	12	35.429	1	<.001
	No	52 (52.5%)	47 (47.5%)				
History of Hypertension	Yes	75 (76.5%)	23 (23.5%)	16	0.685	1	.408
	No	66 (70.2%)	28 (29.8%)				
History of Diabetes	Yes	35 (74.5%)	12 (25.5%)	18	0.000	1	1.00
	No	105 (73.4%)	38 (26.6%)				
History of Myocardial Infarction	Yes	28 (77.8%)	8 (22.2%)	14	0.164	1	.686
	No	115 (72.8%)	43 (27.2%)				
History of Angina	Yes	15 (75%)	5 (25%)	16	0.000	1	1.00
	No	12 (63.3%)	46 (26.7%)				

*Continuity correction reported where expected frequencies <5

**n=2 cases with missing angiography data

Table 35 Age and key prehospital timings for patients undergoing angiography

Median	Angiography performed		U*	z	p value
	Yes	No			
Age (years)	64 (22-91)	78 (46-96)	6798.5	6.717	<.001
Time to ROSC (minutes)	24 (6-87)	26 (5-59)	4675.5	1.331	.183
Call to arrival of first resource (minutes)	6 (1-48)	5 (1-19)	3801.0	-1.124	.261

*Mann-Whitney test

6.15 Clinical characteristics of patients exposed to mild therapeutic hypothermia

Similarly, significantly higher proportions of male patients (57.4%, n=81 versus 30.4%, n=17, p<.001) and those who presented in a shockable versus non-shockable rhythm (62.8%, n=81 versus 25.0%, n=17, p<.001) were exposed to mild therapeutic hypothermia (Table 36). Median age was also lower in patients undergoing this treatment (median 63 years versus 73 years, p<.001) (Table 37).

Table 36 Demographic and clinical characteristics of patients exposed to mild therapeutic hypothermia

		Mild Therapeutic Hypothermia (n=197)**		Missing Cases	Chi-Square	DF	p value*
		Yes	No				
Gender	Male	81 (57.4%)	60 (42.6%)	12	10.707	1	<.001
	Female	17 (30.4%)	39 (69.6%)				
Witnessed Arrest	Yes	81 (50.0%)	81 (50.0%)	12	0.000	1	1.00
	No	17 (48.6%)	18 (51.4%)				
Bystander CPR	Yes	64 (54.7%)	53 (45.3%)	12	2.362	1	.124
	No	34 (42.5%)	46 (47.5%)				
Shockable	Yes	81 (62.8%)	48 (37.2%)	12	23.948	1	<.001
	No	17 (25.0%)	51 (75.0%)				
Systolic BP <90 mmHg	Yes	6 (37.5%)	10 (62.5%0	12	0.580	1	.435
	No	92 (50.8%)	89 (49.2%)				
Angiography	Yes	89 (63.1%)	52 (36.9%)	13	35.429	1	<.001
	No	8 (14.5%)	47 (85.5%)				
History of Hypertension	Yes	51 (54.8%)	42 (45.2%)	25	1.766	1	.144
	No	40 (44%)	51 (56%)				
History of Diabetes	Yes	18 (43.9%)	23 (56.1%)	27	0.302	1	.484
	No	71 (50.4%)	70 (49.6%)				
History of Myocardial Infarction	Yes	20 (57.1%)	15 (42.9%)	23	0.563	1	.453
	No	73 (48.3%)	78 (51.7%)				
History of Angina	Yes	12 (60%)	8 (40%)	25	0.581	1	.352
	No	79 (48.2%)	85 (51.8%)				

*Continuity correction reported where expected frequencies <5

**n=12 cases with missing hypothermia data

Table 37 Age and key prehospital timings for patients exposed to mild therapeutic hypothermia

Median	Mild Therapeutic Hypothermia		U*	z	p value
	Yes	No			
Age (years)	63 (22-81)	73 (34-96)	7051	5.5	<.001
Time to ROSC (minutes)	24 (5-72)	24 (6-87)	4708	-.112	.911
Call to arrival of first resource (minutes)	6 (2-17)	6 (1-48)	4677	-.439	.661

*Mann-Whitney test

6.16 Odds of good outcome for clinical and demographic variables

The presence of a shockable rhythm (OR 5.920, 95% CI 2.477-14.148), performance of angiography (OR 4.005, 95% CI 1.689-9.497) and initiation of mild therapeutic hypothermia (OR 1.818 95% CI 1.137-2.909) were associated with increased odds of good neurological outcome. Conversely, administration of adrenaline post ROSC was associated with decreased odds of good outcome (OR 0.063 95% CI 0.009-0.445) (Table 38).

Table 38 Unadjusted odds of good versus poor outcome for a range of clinical and demographic variables

	OR	95% CI Lower	95% CI Upper
Male	1.577	0.902	2.757
Failed Intubation	1.187	0.375	3.760
Witnessed Arrest	1.054	0.590	1.883
Bystander CPR	1.531	0.947	2.474
Shockable	5.920	2.477	14.148
Converted to shockable	0.455	0.156	1.333
Advanced Paramedic	0.983	0.451	2.140
Post ROSC Adrenaline	0.063	0.009	0.445
Post ROSC Atropine	0.172	0.025	1.176
Angiography	4.005	1.689	9.497
Mild Therapeutic Hypothermia	1.818	1.137	2.909
History of Hypertension	1.253	0.810	1.939
History of Diabetes Mellitus	0.975	0.589	1.613
History of Previous Myocardial Infarction	0.901	0.507	1.603
History of Angina	0.629	0.255	1.552

6.17 Odds of poor outcome associated with endotracheal intubation

The odds of poor outcome with ETI versus SGA were not significant (Table 39). When patients were stratified by the presence of shockable and non-shockable rhythm, significantly increased odds of poor outcome associated with ETI were observed in the non-shockable group (OR 1.111, 95% CI 1.013-1.279). Of note, there were no cases with good neurological outcome in the ETI group for patients presenting in a non-shockable rhythm.

Table 39 Unadjusted odds of poor outcome with ETI based on final airway approach stratified by presenting rhythm

	OR	**95% CI Lower**	**95% CI Upper**
All Cases	1.107	0.929	1.320
Shockable	1.013	0.738	1.392
Non-shockable*	1.111	1.013	1.279

* n=0 ETI cases in the good outcome group

Repetition of these analyses based on an intention-to-treat approach, where the airway management strategy was classified according to the first airway device employed regardless of whether this was successful, revealed similar trends (Table 40).

Table 40 Unadjusted odds of poor outcome with ETI based on intention-to-treat analysis stratified by presenting rhythm

	OR	95% CI Lower	95% CI Upper
All Cases	1.061	0.521	2.162
Shockable	1.225	0.549	2.734
Non-shockable*	1.094	1.011	1.279

* n=0 ETI cases in the good outcome group

However, the odds of poor outcome associated with ETI were not significant when adjusted for the presence of bystander CPR, witnessed arrest, presence of a shockable rhythm and age (Table 41)

Table 41 Adjusted odds of poor outcome with ETI

	OR	**95% CI Lower**	**95% CI Upper**
All Cases	0.836	0.341	3.130

6.18 Binomial logistic regression models.

In binomial regression analysis incorporating Utstein factors conventionally associated with improved survival, there was no significant relationship between airway management approach and good (CPC 1&2) versus poor (CPC 3-5) neurological outcome (Table 42). The final model encompassing airway approach, witnessed arrest, bystander CPR and presence of shockable rhythm was statistically significant, (χ^2 (4, N=209) =33.152, p<.001), and correctly classified 71.8% of cases. However, shockable rhythm remained the only variable to make a unique statistically significant contribution to the model (Appendix 7).

Table 42 Binomial logistic regression model incorporating final airway approach, witnessed arrest, bystander CPR and presence of shockable rhythm

Variable	**B**	**p**	**Odds Ratio**	**95% Confidence Interval**	
				Lower	**Upper**
Final Airway Approach	-3.22	.391	0.725	0.337	1.561
Witnessed Arrest	-.594	.216	0.552	0.216	1.414
Bystander CPR	.280	.430	1.323	0.660	2.650
Shockable	2.282	<.001	9.798	3.534	27.164

Similarly, airway approach was not significantly associated with outcome in further logistic regression analysis incorporating variables identified as significantly associated with survival in preceding univariate analyses in the current study. Younger age, presence of shockable rhythm and shorter time to ROSC remained significantly associated with increased odds of good neurological outcome (Table 43). The overall model was statistically significant, (χ^2 (4, N=209) =74.795, p<.001), and provided improved prediction of outcome, correctly classifying 80.7% of cases (Appendix 8).

Table 43 Binomial logistic regression model incorporating final airway approach, time to ROSC, shockable rhythm and age

Variable	**B**	**p**	**Odds Ratio**	**95% Confidence Interval**	
				Lower	**Upper**
Final Airway Approach	-1.01	.824	0.904	0.374	2.189
Time to ROSC	-.083	<.001	0.921	0.887	0.955
Shockable	1.831	<.001	6.239	2.228	17.472
Age	-.061	<.001	0.941	0.913	0.971

A final logistic regression model solely incorporating variables significantly associated with increased odds of good neurological outcome and excluding airway management approach (Table 44) was statistically significant, (χ^2 (3, N=209) =74.745, p<.001), and provided marginally superior prediction of outcomes through correct classification of 81.6% of cases (appendix 9).

Table 44 Binomial logistic regression model incorporating time to ROSC, shockable rhythm and age

Variable	B	p	Odds Ratio	95% Confidence Interval	
				Lower	Upper
Time to ROSC	-.083	<.001	0.920	0.887	0.955
Shockable	1.837	<.001	6.276	2.242	17.563
Age	-.060	<.001	0.941	0.913	0.971

6.19 SF-36 Data

Complete SF-36 data were obtained for 25.4% (n=15) of eligible patients judged to have a favourable neurological outcome (CPC 1 & 2). In view of this, analysis of these results was restricted solely to descriptive statistics due to the low response rate and potential for bias. Descriptors for the various domains of SF-36 scoring are shown below (Table 45).

Table 45 SF-36 domain descriptors

Physical Component Summary (PCS)	At lowest	Substantial limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated 'poor.'
	At highest	No physical limitations, disabilities or decrements in well-being, high energy level, health in general rated excellent.
Mental Component Summary (MCS)	At lowest	Frequent psychological distress, substantial social and role disability due to emotional problems, health in general rated 'poor.'
	At highest	Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated 'excellent.'
Physical Functioning	Performance of physical activities such as self-care, walking and vigorous activities.	
Role-Physical (RP)	The degree to which a person's typical role activities (e.g. childcare, job) are limited by physical health.	
Bodily Pain (BP)	Intensity, duration and frequency of bodily pain and limitations in usual activities due to pain.	
General Health (GH)	The beliefs and evaluations of a person's overall health.	
Vitality (VT)	Feelings of energy, the absence of fatigue.	
Social Functioning (SF)	The degree to which a person develops and maintains social relationships (e.g. with family, friends etc).	
Role Emotional (RE)	The degree to which a person' typical role activities (e.g. childcare, job) are limited by emotional problems.	
Mental Health (MH)	A person's emotional, cognitive, and intellectual status	

Individual physical component summary scores ranged from 23.18 to 58.19 and mental component summary scores ranged from 35.9 to 59.35. Mean component summary scores are shown below (Figure 6). Mean scores were marginally above population norms in Mental Component Summary (MCS), Bodily Pain (BP), Vitality (VT), Role Emotional (RE), and Mental Health (MH) domains.

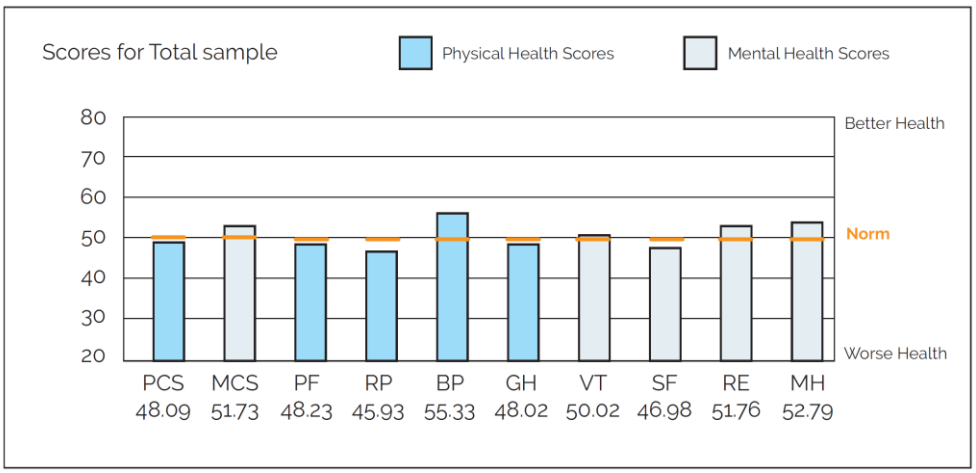

Figure 6 Individual physical and mental component summary scores for responders to the SF-36 survey

The charts below (Figure 7) indicate the percentage of participants with summary and individual component scores above, at or below population norms. In terms of summary scores, a higher proportion of participants achieved Mental Component Summary scores above populations norms when compared with Physical Component Summary scores (47% versus 27%). More than half of participants were judged to have scores above population norms in the domains of Bodily Pain (BP) and Role Emotional (RE). In contrast, the highest proportions of participants with below population norm scores were observed in the Role Physical (40%) and General Health (40%) domains.

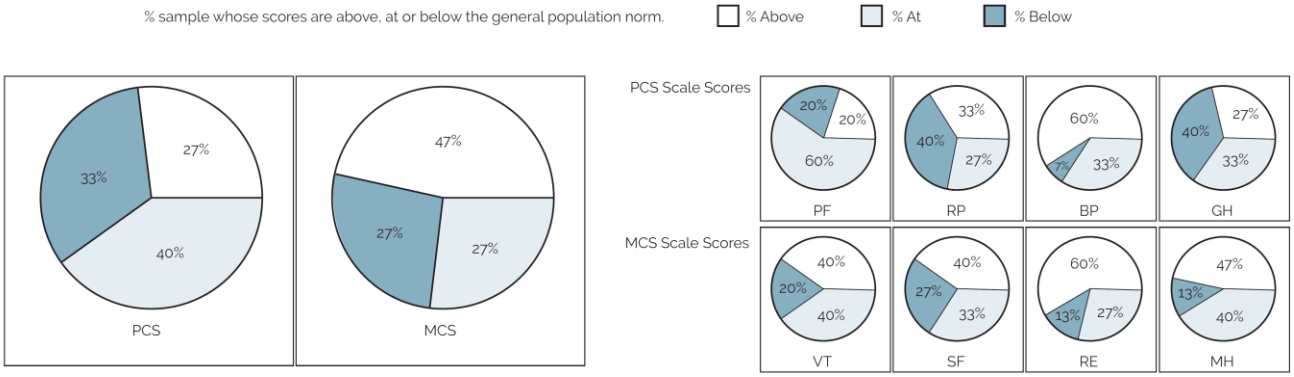

Figure 7 Comparison of participant SF-36 scores with population norms

6.20 Comparison of characteristics of responders versus non-responders to the SF36 survey

There was no significant variation in gender and clinical demographics between SF36 survey responders versus non-responders (Table 46).

Table 46 Comparison of dichotomous demographic and clinical variables between SF-36 responders and non-responders

		SF 36 Completed		Chi-Square	DF	p value*
		Yes (n=15)	**No (n=44)**			
Gender	Male	14 (29.8%)	33 (70.2%)	1.327	1	.249
	Female	1 (8.3%)	11 (91.7%)			
Witnessed Arrest	Yes	12 (24.5%)	37 (75.5%)	0.000	1	1.00
	No	3 (30%)	7 (70%)			
Bystander CPR	Yes	13 (31.7%)	28 (68.3%)	1.818	1	.178
	No	2 (11.1%)	16 (88.9%)			
Shockable	Yes	14 (25.9%)	40 (14.1%)	0.000	1	1.00
	No	1 (20.0%)	4 (80.0%)			
Airway	ETI	3 (23.1%)	10 (76.9%)	0.000	1	1.00
	SGA	12 (26.1%)	34 (73.9%)			
Therapeutic Hypothermia	Yes	10 (27.8%)	26 (72.2%)	0.104	1	.747
	No	4 (20.0%)	16 (80.0%)			
Angiography	Yes	13 (24.1%)	41 (75.9%)	0.060	1	.806
	No	2 (40.0%)	3 (60.0%)			

*Continuity correction reported where expected frequencies <5

Similarly, there was no significant variation in the distribution of age and time-based measures between responders and non-responders (Table 47).

Table 47 Comparison of age and key prehospital timings between SF-36 responders and non-responders

	SF 36 Completed		U*	z	P value
	Yes (n=15)	**No (n=44)**			
Age (years)	63.0 (44.0-85.0)	60.5 (22-82)	305.0	-.435	.663
Arrival of first resource to airway placement (minutes)	8.0 (2.0-20.0)	10.0 (2.0-41.0)	398.5	1.352	.176
Call to arrival of first resource (minutes)	(7.0 (1.0-11.0)	6.0 (1.0-13.0)	320.5	-.166	.868
Arrival of first resource to ROSC (minutes)	16.0 (5.0-34.0)	16.0 (6.0-48.0)	299.0	-.540	.589
Arrival of first resource to departure to HAC (minutes)	46.0 (24.0-83.0)	45.0 (7.0-95.0)	310.0	-.348	.728
Transfer time to HAC (minutes)	24.0 (1.0-43.0)	14.0 (4.0-49.0)	243.5	-1.508	.131

*Mann-Whitney test

6.21 Summary

These results demonstrate that recruitment proceeded as planned, with the number of patients lost to follow up (n=11, 5%) within the range anticipated as part of sample size calculations. Of note, there were no significant differences in demographics and clinical characteristics between the final study sample and patients lost to follow up. The majority of participants for whom complete outcome data were available were male (n=149, 71.3%), presented in a shockable rhythm (n=135, 64.6%), suffered a witnessed cardiac arrest (n=172, 82.3%) and had bystander CPR performed n=125, 59.8%). Median age was 67 years (range 22-96). Airway management was most commonly undertaken using a supraglottic device (n=152, 72.7%). Patients were attended within a mean 6.5 minutes (SD 4.1) of the emergency call and mean time from arrival at scene to commencement of transfer to a HAC was less than an hour (56.3 minutes, SD 19.5). The most common indication for transfer to a HAC was the presence of ST elevation (n=176, 84.1%). Once admitted to a HAC, higher proportions of patients with LBBB (n=9, 75%) and ST elevation (n=129, 73.7%) underwent angiography compared with those demonstrating ST depression alone (n=12, 63.2%), although this variation was not significant (p=.608). These results are key in facilitating comparison of sample characteristics with those of other out-of-hospital airway management and cardiac arrests studies.

Higher proportions of patients with good neurological outcome (CPC1 & 2) presented in a shockable rhythm (n=54, 91.5% versus n=81, 54.0%, p<.001) and underwent angiography (n=54, 91.5% versus n=97, 65.5%, p<.001). Median age (61 years versus 69 years, p<.001), and time to ROSC (16 minutes versus 27 minutes, p<.001) were lower in patients with good outcomes, whereas there was no significant difference in response times or duration of HAC transfer. There was also no significant variation between the good versus poor outcome groups in the proportions of patients who suffered a witnessed cardiac arrest or had bystander CPR performed. Conversely, significantly higher proportions of patients in the poor outcome group experienced post ROSC hypotension (n=17, 11.3% versus n=0.0, 0%, p=.016) and had post ROSC adrenaline administered (n=45, 30.0% versus n=1, 1.7%, p<.001). The low response rate (n=15, 25.4%) achieved via telephone administration of the SF36 survey to patients with good outcome (CPC 1&2) meant that further statistical analysis was inappropriate. However, these results do demonstrate that a proportion of patients in the study sample survived out-of-hospital cardiac arrest with mental and physical component scores above population norms.

Overall, unadjusted odds of poor outcome associated with ETI versus SGA were not significant (OR 1.061, 95% CI 0.521-2.162). Odds of poor outcome associated with ETI were significant for patients presenting in a non-shockable rhythm (OR 1.111, 95% CI 1.013-1.279), however this finding was not

replicated in multivariate analysis controlling for the presence of bystander CPR, witnessed arrest, presence of a shockable rhythm and age (adjusted OR 0.836, 95% CI 0.341-3.130). Airway management remained insignificant as a predictor variable in multiple binomial logistic regression models designed to predict good versus poor outcome. The following chapter presents a review and critical analysis of these results, comparing and contrasting findings in the context of national and international studies relating to both the influence of airway management on mortality and morbidity, and the role of clinical and demographic factors in predicting outcomes within the wider resuscitation literature.

7. Discussion of Results

7.1 Introduction

This section commences with a critical review of the sampling procedure and cases lost to follow up, comparing sample demographics and clinical characteristics with other studies addressing airway management in out-of-hospital cardiac arrest. Consideration is also given to the proportions of patients exposed to different airway management techniques and how this distribution compares with other studies. Key themes and factors influencing outcomes are reviewed sequentially, comparing and contrasting findings with the wider out-of-hospital resuscitation literature and highlighting unique contributions made by the current study in specific areas, such as the influence of time to ROSC as a potential confounder in airway management research and the newly emerging subset of patients converting to a shockable rhythm during resuscitation. Finally, the influence of airway management on outcomes in the current study is summarised and considered in the context of the wider resuscitation literature.

7.2 Sampling

The target sample size (n=220) was recruited within the allotted timeframe. The sampling method was based on established procedures within the host EMS system used to provide cardiac arrest registry data, modified to alert the researcher to cases fulfilling study inclusion criteria. However, there is potential for staff responsible for maintenance of registry data to have missed potentially suitable cases. Complete outcome data in the form of assessment of neurological function via CPC scoring was achieved for 209 patients. This resulted in 5% of cases being lost to follow up, although the target sample size was increased by approximately 10% at the outset to account for the anticipated challenges associated with obtaining complete outcome data. This approach was based on an RCT comparing prehospital paramedic RSI with advanced airway management delayed until hospital arrival in head injured patients (Bernard, Nguyen, et al., 2010), where the target sample size was increased by 20% to account for lost cases but ultimately achieved complete follow up in all but 4.2% of patients (n=13). Although Bernard et al. employed more sophisticated functional measures at 6-months post discharge, the inability to assess outcome in 5% of cases in the current study appears broadly consistent with this experience. Comparison of the proportion of cases lost to follow up with other cardiac arrest studies is problematic due to variable approaches in reporting. Certainly the level of follow up achieved compares favourably with a reported 16% (n=48) of patients in whom neurological outcome was unknown in a retrospective North American study (Egly et al., 2011). Tanabe and colleagues reported an absence of neurological outcome data one month post discharge in <0.3% (n=368) of cases in a Japanese prospective nationwide database study,

however many patients were excluded due to an inability to determine whether advanced airway management had been performed (n=2,169) or the type of advanced airway device used (n=340) (Tanabe et al., 2013). Larger registry based studies which are reliant on reporting from multiple individual EMS agencies do not generally report the number of cases where neurological outcome measures are absent (Wang et al., 2012). However, the CARES registry investigators excluded 14.7% (n=1,847) of cases where the airway management approach could not be determined and therefore regardless of whether neurological outcomes were known for these patients their data could not contribute to the final analysis (McMullan et al., 2014). In contrast, the airway management approach could be determined for all cases recruited as part of the current study and there was no significant variation in key clinical and demographic variables between included versus excluded cases.

7.3 Sample demographics and clinical characteristics

The inclusion and exclusion criteria defined at the outset of this study were designed to enable recruitment of a specific sample characterised by direct transfer to a HAC following prehospital ROSC after treatment incorporating advanced airway management. Given that there are no existing studies specifically addressing the influence of advanced airway management on outcomes in this sub-set of patients, comparisons with results drawn from other airway management studies or research incorporating more general resuscitation populations should be made with caution. In some airway management studies, particularly those utilising multi-site registry data, demographic data are not fully reported and therefore only limited or no comparisons are possible (Wang et al., 2012; McMullan et al., 2014). In contrast, comparatively extensive demographics are reported in studies addressing outcome prediction in cardiac arrest, however the samples in these are usually drawn from more general resuscitation populations (Abrams et al., 2011; Kaji et al., 2014; Terman et al., 2015; Whittaker et al., 2016). An important exception to this is the Harefield Cardiac Arrest Study, which was conducted in an individual HAC that also participated in the current study (Iqbal et al., 2015).

Despite these limitations, several trends identified within the current study are broadly comparable with other research findings. The majority of patients were male (67.7%, n=149) with mean and median ages of 66.8 (22-96) and 67 (SD 13.1) respectively. This is in keeping with findings from the Harefield study, where the majority of patients were male (79.9%) and median age was 65 (IQR 56-65) (Iqbal et al., 2015). Similarly, studies from the wider resuscitation literature report proportions of male patients ranging from 54%-72% and median ages of 65-72 (Arslan Hanif et al., 2010; Studnek et al., 2010; Tanabe et al., 2013). In the context of the current study, the predominance of older

male patients is likely a reflection of the specific study sample under consideration, given that risk of acute coronary syndrome increases with age and is more prevalent in males (Hasan et al., 2014). In terms of clinical characteristics, the majority of patients suffered witnessed cardiac arrest (n=172, 82.3%) and an appreciable proportion received bystander CPR (59.8%). More than half presented in a shockable rhythm (n=135, 64%). Although a similar proportion of patients in the Harefield study suffered a witnessed cardiac arrest (92%), comparatively higher proportions received bystander CPR (79.3%) and presented in a shockable rhythm (82.8%) (Iqbal et al., 2015). This is an important consideration when comparing outcome data given the association of these variables with more favourable outcomes (Sasson et al., 2010). In another UK resuscitation study investigating outcomes for all cardiac arrest cases transferred to an Emergency Department over a five-year period, the arrest was witnessed in 71% (n=250) of patients and bystander CPR performed in 65% (n=226). A shockable rhythm was documented during the prehospital phase in 55% (n=193) of cases (Whittaker et al., 2016).

Earlier research investigating the influence of bystander CPR on outcomes in a series of North American patients (n=727) identified that provision of resuscitation prior to the arrival of EMS increased the proportions of patients found to be in a shockable rhythm (80.9% versus 61.4%) and significantly increased adjusted odds of the presence of VF on EMS arrival (OR 2.7 95% CI 1.7-4.4). There was no significant difference in response times between the bystander CPR and no bystander CPR groups (Swor et al., 1995). More recent analysis from a larger cohort of out-of-hospital cardiac arrest patients in Sweden (n=30,381) similarly reported higher proportions of patients presenting in VF where bystander CPR was performed (41.3% versus 30.7%) (Hasselqvist-Ax et al., 2015). It may therefore be that higher rates of VF observed in the Harefield study are at least in part the product of higher rates of bystander CPR. Shorter ambulance response times have also been associated with higher proportions of patients presenting in a shockable rhythm. Although response times were not reported in the Harefield study, the current study identified no significant differences in median time to arrival of EMS between patients with good versus poor outcome. Other investigators have identified variation in socioeconomic status between different geographical areas as a significant predictor of the likelihood of bystander CPR following out-of-hospital cardiac arrest in both UK (Moncur et al., 2016) and North American (Vaillancourt, Lui, De Maio, Wells, & Stiell, 2008) populations. Previous cardiovascular research relating to stroke in London highlights significant variation in socioeconomic status between different geographical areas and a statistically significant relationship between lower status and poorer outcomes (Chen, McKevitt, Rudd, & Wolfe, 2014). Higher rates of bystander CPR in the Harefield study may therefore also be reflective of population demographics and socioeconomic status when compared with the current study which was a multi-

centre pan London programme of research. In the international literature specifically addressing airway management, rates of witnessed arrest range from 40.1-65.8% with bystander CPR in 39.4-73.9% and a shockable rhythm in 8.1-28% (Arslan Hanif et al., 2010; Studnek et al., 2010; Tanabe et al., 2013). In other studies incorporating more general out-of-hospital resuscitation populations, corresponding values are 65.4-77% witnessed arrest, 32-36.7% bystander CPR and 30.5-36% of cases presenting in a shockable rhythm (Fridman et al., 2007; Kaji et al., 2014). Given the relatively high rates of witnessed and shockable arrests observed in the current study, rates of bystander CPR are somewhat lower than the upper ranges reported above.

7.4 Distribution of airway management approach

The proportion of patients managed via a SGA device (n=152, 72.7%) versus ETI (n=57, 27.3%) was comparatively higher in this dataset than that observed in a number of other studies investigating the influence of airway management on outcome in cardiac arrest. Studies conducted in North American paramedic systems report ETI rates in cardiac arrest ranging between 52.6% to 86.2% (Arslan Hanif et al., 2010; Egly et al., 2011; Wang et al., 2012), with lowest rate of ETI observed in the most recent of these (McMullan et al., 2014). Secondary analysis of results from the ROC PRIMED trial revealed that of 10,455 adult out-of-hospital cardiac arrest cases, 81.2% (n=8,487) received ETI and 18.8% (n=1,968) underwent SGA insertion (Wang et al., 2012). Corresponding values from the Cardiac Arrest Registry to Enhance Survival (CARES) were 52.6% (n=5,591) ETI and 29.3% (n=3,110) SGA, with the remaining 18.2% (n=1,929) receiving no form of successful advanced airway placement (McMullan et al., 2014). Appreciably lower rates of ETI use ranging from 4.7% to 22.2% are reported from studies conducted in evolving Asian EMS systems (Takei et al., 2010; Kajino et al., 2011; Shin et al., 2012; Hasegawa et al., 2013). However, the low rates of ETI use in these settings are not matched by a concomitant increase in the use of SGA devices as seen in North American studies, rather the majority of patients are managed by basic means alone. Indeed, analysis of the All-Japan Utstein Registry identified that basic airway measures with bag-valve-mask ventilation alone formed the mainstay of management in 43% (n=281,522) of patients, with 37% (n=239,550) undergoing SGA insertion and 6% (41,972) receiving ETI (Hasegawa et al., 2013).

The increased use of SGA devices observed in the current study may be the result of a number of factors. Endotracheal intubation was not routinely available to all paramedics and other ambulance clinicians undertaking resuscitation during the study period and it was not known whether an intubation trained paramedic attended the scene, with the exception of cases managed by Advanced Paramedic Practitioners who are all permitted to perform this skill. There remains considerable scientific equipoise globally as to the most appropriate approach to airway management in cardiac

arrest, and there have been calls specifically within the UK for increased use of SGA devices rather than ETI in prehospital airway management for cardiac arrest (Deakin, Clarke, et al., 2010) coupled with an observed reduction in the availability of intubation training opportunities (Deakin, King, & Thompson, 2009).

Meaningful comparisons between other EMS systems and the UK setting are problematic. Large registries incorporate data from a number of individual services that may vary in terms of clinical guidelines or protocols, level of on-line versus off-line medical direction, levels of education and training and response model (Pozner et al., 2004; Black & Davies, 2005; Lockey, 2009). Whilst the principles of orotracheal intubation and associated equipment remain relatively universal, the range of supraglottic airways employed by different agencies in different studies is considerable (Ostermayer & Gausche-Hill, 2014). A number of SGAs are not in use within the UK, and there is considerable variation in success rates and insertion times between different devices (Duckett et al., 2013; Middleton et al., 2014). In addition, the majority of these studies include cardiac arrests from a variety of medical and traumatic aetiologies rather than examining a specific subset of patients such as those recruited into the present study. Nonetheless, comparison of results with international studies suggests proportionally higher SGA use in this cohort than in North American systems.

7.5 Factors influencing outcome – prehospital timings

A potential strength of the current study is that time intervals from arrival to successfully establishing an advanced airway and achieving ROSC are recorded, alongside any failed attempts at intubation. The absence of this data in registry studies is acknowledged as a confounding factor in outcome analyses (McMullan et al., 2014). There is potential for bias in favour of improved outcomes from ETI if SGAs are predominantly used as rescue devices following failed intubation attempts rather than as the primary means for establishing an advanced airway, as in the current study. In addition, Kim and colleagues noted delayed time to ROSC during emergency department management of patients with a failed prehospital intubation attempt (Kim, Kim, et al., 2014). Although the current study found no significant difference in mean time to placement of an advanced airway between those with good versus poor outcome, a recent in-hospital analysis of cardiac arrest airway management practices found increased odds of 24-hour survival (adjusted OR 0.94, 95% CI 0.89-0.99) when the interval to advanced airway placement was <5 minutes versus >5 minutes (Wong, Carey, Mader, & Wang, 2010). The current study identified no significant difference in median time to advanced airway placement between the good (10 minutes) versus poor (11 minutes) outcome groups (p=.462), albeit median time to airway placement was longer than in the

<5 minutes cohort identified by Wong et al. in the in-hospital population. Although the aetiology of cardiac arrest and clinical response profiles between hospital and out-of-hospital cardiac arrest populations may vary, this evidence supports the routine collection of key prehospital timings as part of the current study.

7.6 Time to ROSC

The current study demonstrated shorter median time from arrival to ROSC in the group with good neurological outcome. This finding is consistent with data from the Harefield study which reported a median duration of resuscitation of 4 minutes in patients with good functional outcome at discharge versus 16 minutes in those with poor outcomes (p<.001) (Iqbal et al., 2015). Two recent studies have examined predictors of good neurological outcome (CPC 1&2) in a cohort of patients (n=227) with ROSC and subsequent ITU admission following cardiac arrest of presumed cardiac aetiology treated by emergency medical technicians (EMTs) in Tokyo (Komatsu et al., 2013) and a larger cohort of patients with prehospital ROSC (n= 17,238) derived from a national registry incorporating all patients treated by EMTs in Japan (Goto et al., 2016). Although the scope of practice of these providers varies from that of UK ambulance clinicians, some Japanese EMTs are permitted to undertake advanced airway management and administer intravenous adrenaline. In this setting, investigators found that the only independent factor associated with good neurological outcome was shorter time from receipt of call to ROSC (OR 0.86, 95% CI 0.81-0.92, p<.001). The larger nationwide study reported time to ROSC was inversely associated with good neurological outcome (CPC 1&2) at one month (adjusted OR 0.95, 95% CI 0.94-0.95). Median time to ROSC varied according to presenting rhythm, with the shortest times observed in patients presenting in a shockable rhythm (10 minutes) followed by PEA (14 minutes) and asystole (19 minutes).

A further study investigating duration of resuscitation in arrests witnessed by the attending paramedic identified that although median duration of resuscitation for all cases was 12 minutes, median time was significantly lower in those who survived to discharge (2 minutes versus 24 minutes, p<.001). Logistic regression identified that every one-minute interval increase in duration of CPR was associated with a 13% reduction in the odds of survival to discharge (OR 0.87, 95% CI 0.84-0.89, p<.001) (Nehme, Andrew, Bernard, & Smith, 2016). In view of this, it is somewhat surprising that few studies examining the influence of airway management approach on outcomes in cardiac arrest report time to ROSC as a key variable, (Arslan Hanif et al., 2010; Studnek et al., 2010; Nagao et al., 2012; Tanabe et al., 2013), especially where multivariate regression analyses are performed (Wang et al., 2012; McMullan et al., 2014). Although some studies report total duration of arrival at scene to hospital time, this is not a substitute for time to ROSC as a multitude of factors

and challenges including location of arrest, availability of resources and patient demographics can influence time spent at scene and clinical management (Prekker et al., 2014). In a single study addressing the influence of airway management on outcome, median time to ROSC was higher in patients undergoing advanced airway management than those managed via basic methods alone (14 minutes versus 6 minutes) (Hasegawa et al., 2013) highlighting the potential for confounding in subsequent statistical analysis. The ability to incorporate time to ROSC in binomial regression analysis is therefore a strength of the current study.

7.7 Gender

Although a trend towards a higher proportion of good outcomes in male patients was observed, this was not statistically significant (p=.093). Male gender was not significantly associated with improved outcomes in the Harefield Cardiac arrest study (Iqbal et al., 2015), although it is important to note that this may simply reflect the specific characteristics of datasets solely comprising patients who achieved ROSC and underwent direct transfer to a HAC. In one study of outcomes stratified according to airway management approach, male gender was negatively associated with prehospital ROSC (OR 0.66, 95% CI 0.49-0.89) (Studnek et al., 2010). Statistical modelling of survival based on the Victorian Ambulance Cardiac Arrest Registry identified a negative association between male gender and survival to hospital discharge (OR 0.75, 95% CI 0.54-0.99) (Fridman et al., 2007). A review of the influence of gender on outcomes for patients recruited as part of the North American Resuscitation Outcomes Consortium (ROC) found that unadjusted odds of survival to discharge were lower for women (OR 0.69, 95% CI 0.60-0.77) but that this difference was not significant following adjusted analysis controlling for Utstein survival predictors (OR 1.16, 95% CI 0.98-1.36). When this adjusted analysis was repeated exclusively for patients aged 15-45 years, female gender was significantly associated with improved survival (OR 1.66, 95% CI 1.04-2.64), which the authors suggest is supportive of the cardio-protective effect of hormones in premenopausal women (Morrison et al., 2016). This finding has limited applicability to the current study given the relatively higher median age of female patients (71 versus 66 years), and may provide some explanation as to why no significant variation in outcome according to gender was observed. Equally the current study solely investigated patients with ROSC and did not address patients in whom resuscitation was terminated in the out-of-hospital phase, therefore the lower proportion of female patients could reflect the fact that less female patients experienced prehospital ROSC and thus fewer were eligible for enrolment.

7.8 Response Times

Shorter response time was not significantly associated with good neurological outcome in either the current study or the Harefield Cardiac Arrest Study (p=.10) (Iqbal et al., 2015). Survival modelling based on data retrieved from the Cardiac Arrest Registry to Enhance Survival (CARES) database demonstrated both a beneficial effect of a response time of less than four minutes and a detrimental effect of a response time in excess of eight minutes in cardiac arrests of presumed cardiac aetiology, although this analysis was designed to provide a composite model of survival rather than predict longer term neurological outcome or quality of life (Abrams et al., 2013). Modelling based on the Victorian Cardiac Arrest Registry found that an extended response time of fifteen minutes and above was not significantly associated with survival in all presenting rhythms (OR 1.02, 95% CI 0.98-1.06) but a response time of less than fifteen minutes was a significant predictor of survival in patients presenting in shockable rhythms only (0.91, 95% CI 0.86-0.96). Furthermore, delays in response time reduced the benefits of both shockable rhythm and bystander CPR on the basis that for every minute of delay the odds of survival declined by 9% amongst patients with a shockable rhythm and by 5% amongst those receiving bystander CPR (Fridman et al., 2007). In contrast to the mixture of urban and rural locations served by ambulance services within the state of Victoria, the population served by the London Ambulance Service is exclusively urban and suburban. The median response time in the current study was six minutes and very few patients waited longer than 15 minutes for the arrival of the first ambulance resource. Response times are frequently associated with survival in the wider resuscitation literature (Abrams et al., 2011) and form part of mandatory reporting as per Utstein requirements (Perkins et al., 2015) and it is therefore likely that the lack of association between response times and outcome in the current study simply reflects the fact that only patients who achieved prehospital ROSC were recruited and therefore were likely to have benefited from shorter response times anyway. Certainly the higher proportion of patients presenting in a shockable rhythm would bear this out.

7.9 Bystander CPR

A larger proportion of patients with good versus poor neurological outcomes received bystander CPR, although this was not statistically significant (69.5%, n=41 versus 56.0%, n=84, p=.102). However, it is important to note that the current data set is based on patients who experienced prehospital ROSC and it may be that bystander CPR would be a more important predictor of survival in a more generic resuscitation population incorporating patients who did not achieve ROSC or had resuscitation attempts terminated in the field. Equally bystander CPR has been demonstrated to prolong the presence of ventricular fibrillation and tachycardia (Fridman et al., 2007). Interestingly, in composite survival modelling derived from CARES registry data, the predicted contribution of

bystander CPR to improved survival was most pronounced in witnessed cases presenting in a shockable rhythm (Abrams et al., 2013). Given that the presence of a shockable rhythm was significantly associated with good neurological outcome in the current study, this may in part account for the non-significant trend towards improved outcomes in those who received bystander CPR.

7.10 Age

Younger age was consistently associated with good neurological outcomes in both univariate and multivariate analyses. This is consistent with a systematic review of survival after resuscitation from out-of-hospital cardiac arrest in the elderly incorporating participants aged ≥70 years which reported pooled overall survival to discharge to be 4.1% (95% CI 3.0-5.6 %; range 0-9.0%) (van de Glind et al., 2013). A further systematic review investigating outcomes across all age groups identified an overall pooled survival rate of 7.6% (95% CI 6.7-8.4%) (Sasson et al., 2010). Both reviews identified that outcome data relating to subsequent longer term neurological function and quality of life in older survivors were lacking and highlighted the important distinction between chronological and physiological or biological age in prognostication.

Since then, two further studies have investigated the role of comorbidities in addition to age in older cardiac arrest survivors in American (Terman et al., 2015) and Norwegian (Libungan et al., 2015) populations. Terman et al. found that age remained a significant predictor of poor neurological outcome in both unadjusted (OR 0.78, 95% CI 0.70-0.88) and adjusted (OR 0.79 95% CI 0.67-0.94) analyses incorporating Charlson Comorbidity Index scoring. Similarly, Libungan et al. found that 30-day survival stratified according to ten-year age intervals declined from 6.7% in those aged 70-79 to 2.4% in those aged over ninety years, although the proportion of patients presenting in a shockable rhythm, which is an established predictor of survival, declined with age. Despite this, the distribution of CPC scores was similar between age groups, leading the authors to conclude that age alone is an insufficient predictor of long term neurological outcome in survivors. Although the current study sought to collect data relating to variables such as hypertension and heart disease, these data were incomplete and therefore further analysis incorporating comorbidities was not appropriate. In addition, it is important to note that although median age was significantly higher in patients with poor neurological outcome, the oldest survivor with good neurological outcome was 85 years of age. This lends support to the notion that age is alone is insufficient for reliable prognostication.

7.11 Temperature

Temperature measured via a tympanic thermometer in the prehospital phase was not a significant predictor of outcome. Data from animal and clinical trials suggests that an initial period of hypothermia often occurs spontaneously after resuscitation which may be followed by a later period of hyperthermia. Prevention of this initial hypothermic phase is associated with worsened outcomes (Hickey et al., 2003). The development of hyperthermia post ROSC is an established predictor of worsened outcomes following cardiac arrest (Takino & Okada, 1991; Langhelle et al., 2003). Current resuscitation guidelines define fever as temperature ≥37.6^{o}C and advocate a target temperature of 36^{o}C for post cardiac arrest temperature control (Nolan et al., 2015). In the current dataset, mean temperature was 35.2^{o}C for 147 patients where a tympanic thermometer was used. Only one patient had a tympanic temperature of ≥37.6^{o}C and a further fourteen had temperatures >36^{o}C.

These findings are consistent with data reported from an observational study investigating temperature in out-of-hospital cardiac arrest patients in Scotland using oesophageal temperature probes (Lyon, Richardson, et al., 2010). Mean temperature measured in patients during the prehospital phase (n=29) was 33.9^{o}C (95% CI 33.2-34.5) and 34.3^{o}C (95% CI 34.1-34.6) in those where measurement was performed on arrival in the ED (n=164). In keeping with these findings, the mean temperature of 35.2 ^{o}C identified in the current dataset indicates that the majority of patients did not experience post ROSC fever in the prehospital phase. Although the use of an oesophageal temperature probe provides a more reliable measure of core temperature, other studies suggest that tympanic thermometers provide a reasonable approximation of core temperature (Moran et al., 2007) including during induction of therapeutic hypothermia (Hasper, Nee, Schefold, Krueger, & Storm, 2011). The lack of patients experiencing post ROSC fever in this cohort may be attributable to early temperature measurement in the prehospital phase given the immediate spontaneous hypothermia observed in some animal and clinical studies. Lyon et al. observed marginally higher mean temperature where oesophageal measurement was undertaken on ED arrival versus during the prehospital phase (Lyon, Richardson, et al., 2010) however none of these values would have met standard criteria for post ROSC fever. Similarly, an RCT conducted in Australia comparing induction of therapeutic hypothermia prehospital (n=82) versus on ED arrival (n=81) found that mean tympanic temperatures before cooling were 35.8 ^{o}C (95% CI 35.5-36.1) and 35.9 ^{o}C (95% CI 35.7-36.2) respectively. On the basis of current targeted temperature management approaches none of these patients would require aggressive cooling if treated as per contemporary guidelines (Nolan et al., 2015). The current study methodology did not make provision for recording temperature during subsequent phases of the clinical pathway, therefore the proportion of patients who developed fever during in-hospital management and the effect of this on outcome is unknown. Nonetheless,

the absence of fever as per guideline definitions in all but one of the study participants may provide some explanation as to why mean prehospital temperature did not vary significantly between survivors with good versus poor outcome.

7.12 End tidal CO_2

Results from $ETCO_2$ monitoring demonstrated significantly lower median $ETCO_2$ values in patients with good versus poor neurological outcome (4.4 kPa versus 4.8 kPa, p=.042). This relationship persisted when $ETCO_2$ values were analysed by individual CPC category (p=.047), with the highest median $ETCO_2$ observed in patients categorised as CPC 5 (5.5 kPa). Patients in the CPC5 group also demonstrated the widest variation in $ETCO_2$ values (1.3-13.3 kPa). There was no significant difference in median $ETCO_2$ between the ETI and SGA groups (4.1 kPa versus 4.3 kPa, p=.825). The majority of existing studies investigating the prognostic role of $ETCO_2$ in resuscitation compare patients who achieved ROSC versus those who did not in order to define $ETCO_2$ thresholds indicative of futility, whereas the current study only addressed patients who achieved ROSC out-of-hospital and therefore cannot be used to define parameters for termination of resuscitation. A prospective observational study of 737 cases of out-of-hospital cardiac arrest in a European physician-led EMS system found that an $ETCO_2$ value of >1.9 kPa after 20 minutes of ALS resuscitation identified those who would subsequently achieve ROSC with 100% sensitivity and specificity (Kolar et al., 2008). Similarly, a smaller (n=27) study conducted in a North American paramedic staffed service noted significantly higher $ETCO_2$ values in patients who achieved ROSC versus those who did not, but was underpowered to identify an $ETCO_2$ threshold indicative of futility (Asplin & White, 1995). Clinicians in both studies utilised mechanical ventilators, thus ensuring the delivery of regular rate and tidal volume whereas patients in the current study were manually ventilated which may have led to more pronounced variation in ventilation patterns and volumes.

Many factors can affect $ETCO_2$ values, including the pre-morbid condition of the patient, physiological stability at the point of ROSC, time at which observations are recorded, ventilation strategy and pharmacological and other clinical interventions (Pokorna et al., 2010). A prospective observational study of 150 patients undergoing out-of-hospital resuscitation by paramedics identified that initial $ETCO_2$ levels were unreliable in predicting survival as lower values were not infrequently recorded immediately after commencement of resuscitation in some patients who subsequently experienced ROSC (Levine et al., 1997). In keeping with the findings reported by Kolar et al. (2008), Levine and colleagues recommend that prognostication should only be undertaken on the basis of values recorded after 20 minutes of ALS. A retrospective review of clinical notes in a physician EMS system identified that patients with stable ROSC frequently exhibited a sudden and

sustained rise in $ETCO_2$ at the point at which spontaneous circulation was restored (Pokorna et al., 2010). Experimental animal studies have documented decreases in $ETCO_2$ associated with adrenaline administration in cardiac arrest (Lindberg, Liao, & Steen, 2000; Burnett et al., 2012). A small observational clinical study (n=20) observed decreases in $ETCO_2$ three minutes after adrenaline administration by a physician team during cardiac arrest, although larger doses of adrenaline were used than those currently recommended (Soar et al., 2015) and the study incorporated a wide range of ages and aetiologies (Cantineau et al., 1994). Nonetheless, the potential for adrenaline administration to affect $ETCO_2$ levels cannot be ignored. Standardised clinical notes completed by ambulance clinicians in the current study provide for a maximum of two $ETCO_2$ values to be recorded, although continuous waveform capnography is routinely available to all providers. These values are entered manually and therefore it is not possible to observe trends in $ETCO_2$ throughout the prehospital phase of care, or to reliably examine the potential effects of clinical interventions on fluctuations in $ETCO_2$ values.

The deleterious effects of hyper and hypoventilation on neurological outcomes are well established in prehospital care (Davis et al., 2004; Bobrow & Ewy, 2009). It may be, therefore, that some of the patients in the CPC5 group were exposed to potentially injurious ventilation strategies and this is reflected in the wide range of $ETCO_2$ values observed. Equally it may reflect a greater degree of physiological derangement during the prehospital phase of care which might reasonably be expected to correlate with poorer outcomes. Only three patients in the current study exhibited $ETCO_2$ values below the ≤1.9 kPa threshold identified as indicative of futility by Kolar and colleagues, all of whom were in the CPC5 group. In the remaining CPC groups, the lowest $ETCO_2$ value recorded was 2.5 kPa. The finding that median $ETCO_2$ values were higher in patients presenting in non-shockable versus shockable rhythms (5.2 kPa versus 4.5 kPa, p=.032) is consistent with evidence from existing observational research, although patients in the non-shockable comparator group in this study were selected on the basis of having suffered cardiac arrest secondary to presumed asphyxial aetiology and these findings may not therefore be directly comparable to patients with evidence of STEMI (Lah et al., 2011). It is hypothesised that the abrupt cessation of circulation associated with the sudden onset of VF or pulseless VT results in a rapid decline in the return of venous blood to the lungs and a consequent reduction in $ETCO_2$ values. In contrast, patients presenting in non-shockable rhythms may have experienced a more gradual decline in the period prior to cardiac arrest and therefore may have been capable of retaining some degree of pulmonary circulation for longer, resulting in higher $ETCO_2$ values on commencement of monitoring (Lah et al., 2011). Certainly a higher proportion of patients presenting in shockable rhythms in the current

study achieved good neurological outcomes, and this may constitute a further explanation for the comparatively lower median $ETCO_2$ values observed in this group.

7.13 Blood pressure

Other indicators of haemodynamic instability including hypotension and the need for post ROSC inotropic support were also associated with poorer outcomes. Median first recorded post ROSC blood pressure was lower in the poor neurological outcome group and demonstrated a wider range of values, although this was not statistically significant (128 mmHg versus 134 mmHg, p=.223). However, all patients who experienced one or more episodes of documented hypotension defined as systolic BP <90 mmHg (n=17) subsequently had poor neurological outcomes (p<.001). In addition, the need for post ROSC adrenaline administration was associated with poor neurological outcomes in all but one of the patients (n=44) who received this intervention (p<.001). These findings are consistent with a number of largescale randomised controlled trials examining the influence of cardiogenic shock on outcomes in STEMI regardless of whether out-of-hospital cardiac arrest was a complicating factor (Hochman et al., 1999; Hochman et al., 2001; Webb et al., 2001; Hochman et al., 2006; Stegman et al., 2012; Bangalore et al., 2015). Multivariate analysis following a retrospective review of 248 patients with acute MI and cardiogenic shock admitted to a Danish PCI centre, of whom 118 (48%) had suffered cardiac arrest, found that 30-day mortality did not differ significantly between the cardiac arrest and non-cardiac arrest cohorts (63% versus 56%, p>.05). In this study, the only predictors of increased mortality in the presence of cardiogenic shock were age (HR 1.02, 95% CI 1.01-1.04, p=.003) and lactate levels on admission (HR 1.06, 95% CI 1.03-1.09, p<.001), which were both higher in the cardiac arrest group (Ostenfeld et al., 2015).

Definitions and thresholds for treatment of cardiogenic shock in the post ROSC phase vary between global resuscitation guidelines applicable to the data collection phase of the current study. The 2010 American Heart Association (Peberdy et al., 2010) and Australian Resuscitation Council (Australian Resuscitation Council, 2006) guidelines recommended treatment of systolic blood pressures <90 mmHg and <100 mmHg respectively, whereas the European Resuscitation Council did not define BP thresholds for treatment favouring other haemodynamic markers such as urine output and lactate levels (Deakin, Nolan, et al., 2010). Post ROSC guidelines used by paramedics in the current study recommend initiation of treatment in the presence of a systolic blood pressure <90 mmHg and concurrent absence of palpable radial pulse. Treatment consists of administration of 250 ml normal saline followed by up to 500 mcg adrenaline intravenously in 100 mcg aliquots titrated to achieve presence of a palpable radial pulse in those patients unresponsive to initial fluid therapy.

An Australian study investigated the influence of blood pressure measured at hospital arrival on outcomes in out-of-hospital cardiac arrest patients with presumed cardiac aetiology who achieved ROSC after treatment by paramedics (Bray et al., 2014). Median systolic BP was 125 mmHg for patients presenting in shockable rhythms (n=2,067) versus 122 mmHg for those with non-shockable rhythms (n=1,269). A higher proportion of patients presenting in non-shockable rhythms had an unrecordable blood pressure or systolic BP <90 mmHg (19% versus 10%, p<.001). For patients in shockable rhythms, a linear decrease in survival was observed for systolic blood pressures <120 mmHg and a significantly decreased adjusted odds of survival for systolic blood pressures <90 mmHg (80-89 mmHg OR 0.49, 95% CI 0.10-0.61; <80 mmHg OR 0.24, 95% CI 0.10-0.61). Adjusted odds of survival were not significantly associated with decreased survival in the non-shockable cohort. It should be noted that this cohort of patients did not consist exclusively of those with presumed STEMI and was recruited from an EMS system with more aggressive intravenous fluid and post ROSC adrenaline therapies and higher blood pressure treatment target (120 mmHg), resulting in a relatively low incidence of hypotension on hospital arrival (14%). Nonetheless, these results lend weight to the notion of worsened outcomes associated with hypotension following prehospital ROSC and raise questions as to whether there is a need for more aggressive post ROSC blood pressure management within the EMS system from which the current study sample was recruited. A potential weakness acknowledged by Bray et al. is that the dose of adrenaline administered could not be determined, however the consistent relationship of hypotension to worsened outcomes despite the aggressive post ROSC inotropic therapy employed in this study suggests that post ROSC adrenaline administration in the current study may constitute a surrogate marker for worsened outcomes due to hypotension rather than an inherently harmful intervention.

7.14 Blood glucose

Mean blood capillary glucose was 9.6 mmol/l and there was no significant variation in mean glucose between participants with good versus poor outcome. Current resuscitation guidelines recommend that blood glucose should be maintained at ≤10 mmol/l and that strict glycaemic control should not be routinely implemented due to the risk of hypoglycaemia (Nolan et al., 2015). On the basis of this threshold for reducing blood glucose, a total of 71 patients would have required intervention to reduce blood glucose to ≤10 mmol/l. However, there was still no statistically significant difference in the proportion of patients with good versus poor outcome when cases were stratified according to whether prehospital blood glucose was ≤10 mmol/l or >10 mmol/l. Secondary analysis of data from a UK study examining outcomes for cardiac arrest patients admitted to intensive care units (ICU) found that the odds of death increased by 1.05-1.08 per 1 mmol/l for blood glucose levels above 7 mmol/l and by 1.21-1.31 for levels below 5 mmol/l (Nolan et al., 2007). Similarly, a retrospective

database review of in-hospital cardiac arrest survivors in American ICUs demonstrated that non-diabetic patients subsequently had decreased adjusted odds of survival where minimum glucose levels were outside the range 3.9-9.4 mmol/l and maximum levels were above 6.2-13.3 mmol/l, whereas reduced odds of survival in diabetic patients were only observed in the context of severe (>13.3 mmol/l) hyperglycaemia (Beiser et al., 2009).

However, blood glucose levels in both studies were measured several hours after cardiac arrest on admission to ICU without reference to prehospital values. A retrospective review of out-of-hospital cardiac arrest patients presenting in VF in a northern European setting linked prehospital cardiac arrest registry data with hospital laboratory records to describe trends in blood glucose immediately after return of spontaneous circulation (Nurmi et al., 2012). Blood glucose did not change significantly between the prehospital phase and hospital admission in survivors with good neurological outcome (CPC1&2) (10.5 ± 4.1 mmol/l versus 10.0 ± 3.7 mmol/l, p=.3483), whereas a higher initial mean blood glucose and a significant increase in admission values was identified in those with poor outcomes (CPC3-5) (11.8 ± 4.6 mmol/l versus 13.8 ± 3.3 mmol/l, p=.0025). Data relating to post-admission blood glucose during the in-hospital phase of care were not collected in the current study, therefore the prevalence of post-admission hyperglycaemia could not be determined. However, it may be that increases in blood glucose above prehospital levels identified both on initial hospital admission and during the subsequent in-hospital course may be a more important indicator of the potential for sustained hyperglycaemia and worsened outcomes. This may in turn provide some degree of explanation as to why prehospital blood glucose levels were not associated with outcomes in the current study.

7.15 Presenting ECG rhythm

The majority of study patients presented in a shockable rhythm (64.6%, n=135), with roughly equal proportions of patients presenting in asystole (18.2%, n=38) and PEA (17.2%, n=36). This represents a comparatively higher prevalence of shockable rhythms than that observed in other more heterogeneous adult out-of-hospital cardiac arrest populations, which range from 6%-67%, with means of 35% and 28% in European and North American studies respectively (Berdowski, Berg, Tijssen, & Koster, 2010). Utstein data reported over a five-year period by the EMS system in which the current study was conducted found that yearly prevalence of VF in witnessed cardiac arrest of presumed cardiac aetiology remained between 35-36% throughout 2007-2012 (Fothergill et al., 2013). In contrast, ventricular fibrillation or pulseless ventricular tachycardia was documented as the presenting rhythm in 82.8% of patients recruited as part of the Harefield study (Iqbal et al., 2015). Other longitudinal studies have reported a decline in the prevalence of shockable rhythms in

out-of-hospital cardiac arrest (Bunch et al., 2004; Vayrynen, Boyd, Sorsa, Maatta, & Kuisma, 2011). Possible explanations for this trend include better management of ischaemic heart disease (Hulleman et al., 2015) resulting in less cardiac arrests of presumed cardiac aetiology (Vayrynen et al., 2011), an increase in the proportion of unwitnessed cardiac arrests (Hulleman et al., 2015) and increased use of implantable cardioverter defibrillators resulting in termination of VF prior to the arrival of rescuers (Hulleman et al., 2012). Given that the current study cohort was recruited exclusively from a population with cardiac arrest of presumed cardiac aetiology with post ROSC evidence of STEMI, this provides a potential explanation for the comparatively high proportion of patients presenting in a shockable rhythm and is consistent with trends observed in the Harefield study (Iqbal et al., 2015).

The presenting cardiac arrest rhythm was ventricular fibrillation or pulseless ventricular tachycardia in 91.5% (n=54) of patients with good neurological outcomes versus 54% (n=81) of those with poor outcomes ($p<.001$). Similar findings were observed in the Harefield study, which identified that 92.6% of patients with good functional status (mRS 0-3) presented in a shockable rhythm versus 70.9% with poor functional status (mRS 4-6). The presence of a shockable rhythm is an established predictor of improved mortality and morbidity (Sasson et al., 2010) and studies specifically addressing the impact of presenting rhythm on survival and functional status at discharge consistently report significantly improved outcomes in patients presenting in ventricular fibrillation or pulseless VT (Meaney et al., 2010; Dumas & Rea, 2012; Mader et al., 2012). However, a small but appreciable proportion of patients with good neurological outcomes in the current study presented in non-shockable rhythms including three cases with asystole (5.1%) and two with PEA (3.4%). A prospective review of long term outcomes amongst survivors of non-traumatic out-of-hospital cardiac arrest in an urban North American EMS system during the period 2001-2009 identified that the presenting rhythm was non-shockable in 31% (n=313) (Dumas & Rea, 2012). The proportion of survivors presenting in non-shockable rhythms increased over time, and further analysis of the same dataset suggests that changes in resuscitation guidelines resulting in improved clinical care may in part be responsible for this trend (Kudenchuk et al., 2012). Overall median survival for all cases was 9.8 years, with one year survival rates of 68% for non-shockable and 88% for shockable rhythms, with corresponding rates at five years of 43% and 74% respectively. The lack of functional outcome data at discharge and over time is a limiting factor in this study. However, these findings suggest that although long term survival may be inferior for patients presenting in non-shockable versus shockable rhythms, the absence of a shockable rhythm is by no means universally indicative of futility.

7.16 Conversion to a shockable rhythm

A proportion of patients who initially present in a non-shockable rhythm may convert to a shockable rhythm during resuscitation (Meaney et al., 2010). In the current study, almost a third of patients who initially presented in a non-shockable rhythm converted to a shockable rhythm (n=22, 29.7%) as indicated by the delivery of one or more shocks during subsequent phases of the resuscitation attempt. Although continuous ECG monitoring records were not available for review, the only indications for delivery of a shock during active cardiopulmonary resuscitation in the pre-ROSC phase are the presence of ventricular fibrillation or pulseless ventricular tachycardia (Soar et al., 2015) and therefore it is reasonable to assume that shocks delivered were in response to the development of these rhythms. In a prospective observational study of in-hospital American Heart Association (AHA) registry data, a shockable rhythm developed in 27% (n=5,145) of adult cardiac arrest patients with a first documented rhythm of PEA and in 25% (n=4,988) of cases where the initial rhythm was asystole (Meaney et al., 2010). In the AHA study, survival to discharge was more likely in patients who remained in a non-shockable rhythm throughout the resuscitation attempt when compared with those who subsequently converted to a shockable rhythm (adjusted OR 1.6, 95% CI 1.44-1.80) following PEA (14% versus 7%) or asystole (12% versus 8%). Secondary analysis of CARES registry data from 2005-2010 identified that 10.4% (n=3,225) of adult out-of-hospital cardiac arrest patients who initially presented in asystole or PEA subsequently developed a shockable rhythm (Mader et al., 2012). This study is of particular relevance as it incorporates registry data previously utilised in airway management outcome research (McMullan et al., 2014), excludes cardiac arrests with presumed non-cardiac aetiology, assumes conversion to a shockable rhythm on the basis of delivery of shocks by EMS responder and reports outcomes via the CPC scale. Unadjusted survival rates between patients who converted to a shockable rhythm versus those who remained in PEA or asystole were similar (4.7% versus 4.1%, p=.08). A higher proportion of patients who presented in a shockable rhythm achieved ROSC (52%) versus those remaining in PEA or asystole (27.3%) and those converting to a shockable rhythm (27.9%). Similarly, survival with good neurological outcome (CPC1&2) was higher in patients presenting in a shockable rhythm (16.8%) when compared with those remaining in PEA or asystole (1.7%) and those converting to a shockable rhythm (1.8%).

In keeping with these findings, the current study identified a non-significant trend towards good neurological outcomes amongst survivors who converted to a shockable rhythm (n=3, 13.6%) versus those who remained in asystole or PEA (n=2, 3.8%). However, these results are based on a relatively small number (n=22) of patients who converted to a shockable rhythm drawn from a study sample consisting exclusively of ROSC patients with evidence of STEMI and proportionally less patients

presenting in PEA or asystole at the outset. The proportion of patients converting to a shockable rhythm was higher than that observed in the out-of-hospital study (Mader et al., 2012) and comparable to that reported in the in-hospital study (Meaney et al., 2010), which included patients with non-cardiac aetiologies. Significant differences have been identified between in-hospital and out-of-hospital cardiac arrest populations (Herlitz et al., 2000; Buanes & Heltne, 2014) which may account for the higher overall proportion of patients who converted to a shockable rhythm and higher survival to discharge rates of patients who remained in asystole or PEA in the in-hospital study compared with the proportion of survivors with good neurological outcome in these cohorts in the out-of-hospital study.

7.17 Adrenaline

The proportion of patients surviving with good versus poor neurological outcomes was significantly lower in patients administered intra-arrest adrenaline (47.5% versus 88.7%, p<.001). However, significant differences in factors known to influence survival were identified between patients who were administered adrenaline versus those not exposed to this intervention. The proportion of patients presenting in a shockable rhythm was lower in the adrenaline group (68.9% versus 91.9%, p<.001) and median time to ROSC was significantly longer (30.2 mins versus 14.5 mins, p<.001). The administration of adrenaline requires that vascular access is obtained to facilitate drug delivery and is an advanced life support technique usually provided solely by paramedics in the ambulance service setting, therefore the skill mix of staff attending the scene may have affected rates and timings of administration. Current guidelines prioritise initiation of basic life support measures over advanced techniques (Soar et al., 2015) and therefore it is also possible that there was no opportunity to escalate treatment to incorporate delivery of adrenaline in patients who achieved ROSC in a timely fashion. Furthermore, adrenaline is given as soon as possible in non-shockable rhythms whereas administration is delayed until a cumulative total of three shocks each delivered at 2 minute intervals have been administered in shockable rhythms (Soar et al., 2015) which may also account for lower proportions of patients receiving the drug in this group. It may therefore be that the administration of intra-arrest adrenaline is a surrogate marker for non-shockable rhythms and resuscitation attempts with longer time to ROSC, both of which are independently associated with poorer outcomes.

Considerable controversy and scientific equipoise exists in relation to the administration of adrenaline in cardiac arrest. Theoretical benefits of adrenaline in cardiac arrest include increased coronary and cerebral blood flow and improved myocardial contractility in the context of ROSC (Soar, 2011). An early experimental animal study involving canine subjects in whom ventricular

fibrillation was induced and external mechanical chest compression initiated concluded that the administration of adrenaline was associated with substantial increases in cerebral and myocardial blood flow (Michael et al., 1984). Prevention or reversal of carotid arterial collapse and vasoconstriction of extracerebral carotid arterial and peripheral vascular beds were identified as the likely mechanisms responsible for improvements in flow following adrenaline administration. However, a more recent experimental study employing a porcine model of cardiac arrest incorporating induction of VF and external mechanical chest compressions concluded that although the administration of adrenaline was associated with increases in large vessel perfusion pressure and flow, this was at the expense of reduced cerebrocortical microvascular blood flow resulting in greater tissue ischaemia (Ristagno et al., 2009).

Results from clinical research addressing out-of-hospital cardiac arrest appear consistent with these findings, with multiple observational clinical studies reporting increased rates of ROSC associated with adrenaline administration but no improvements in hospital admission and survival to discharge (Atiksawedparit et al., 2014). A prospective propensity matched analysis of 417,188 cases of cardiac arrest in a Japanese EMS system identified significantly reduced odds of neurologically intact survival (CPC 1&2) at one month associated with adrenaline (OR 0.31, 95% CI 0.26-0.36) (Hagihara et al., 2012). Similarly, Hayashi et al. identified lower rates of neurologically intact survival in patients administered adrenaline (4.1% versus 6.1%, p=.028) but higher adjusted odds of neurologically intact survival in a subset of patients who presented in VF and were administered adrenaline within 10 minutes (adjusted OR 6.34, 95% CI 1.49-27.02) (Hayashi et al., 2012). However, multivariate analysis of observational data from a Swedish EMS system conducted prior to revised guidelines mandating delayed administration of adrenaline in shockable rhythms found that adrenaline remained an independent predictor of worsened outcome (OR 0.43, 95% CI 0.27-0.66) (Holmberg et al., 2002). In the current study, the majority of cases (n=26, 60.5%) in the CPC1 sub-group were not administered intra-arrest adrenaline. In CPC subgroups 2-5 this trend was reversed, with patients exposed to adrenaline administration accounting for increasingly higher proportions of cases ranging from 68.8% (n=11) in CPC2 to 90.6% (n=161) in CPC5 (p<.001). This lends support to the notion that administration of adrenaline may increase ROSC at the expense of worsened neurological outcomes, although these results should be interpreted with caution given the significant differences in factors known to affect survival between the adrenaline and non-adrenaline cohorts.

7.18 12 Lead ECG diagnosis and outcomes

In the current study, the decision to transfer patients post ROSC to a Heart Attack Centre was made autonomously by ambulance clinicians at the scene on the basis of 12 lead ECG diagnoses and

standardised criteria. The proportion of patients presenting with ST elevation was marginally higher than in the Harefield study (84.1% versus 73.6%), although the Harefield study did not include posterior STEMI as a separate diagnostic category. Given that suspicion of posterior STEMI is initially based on identification of ST segment depression in the precordial leads (Lindridge, 2009), this may provide an explanation for the higher proportion of patients judged to have ST segment elevation in the current study. This prevalence of ST elevation is higher than that observed in a number of other studies which report proportions of patients with ST elevation considered for angiography following out-of-hospital cardiac arrest ranging between 31% to 63% (Anyfantakis et al., 2009; Dumas et al., 2010; Larsen & Ravkilde, 2012; Zanuttini et al., 2013; Garcia-Tejada et al., 2014). However, it is important to note that many of these studies involved physician EMS systems where there may be more latitude for clinical decision making and less reliance on standardised criteria for HAC admission. In keeping with trends in the Harefield study, anterior STEMI constituted the most common diagnosis with relatively few cases of left bundle branch block.

It has been demonstrated that UK paramedics can recognise ST segment elevation with equivalent accuracy to junior emergency department doctors in the classroom setting (Whitbread, Leah, Bell, & Coats, 2002), although this does not equate to clinical diagnosis of STEMI. Trivedi et al. found that paramedics could identify STEMI in a series of ECGs with a sensitivity of 92.6% (95% CI 88.9-95.1) and specificity of 85.4% (95% CI 79.7-89.8) in a USA EMS system (Trivedi, Schuur, & Cone, 2009). Similarly, Cantor et al. reported physician agreement with the diagnosis of Canadian primary care paramedics with comparatively less training in 90% (n=121) of patients with suspected STEMI triaged directly to a regional cardiac catheterisation laboratory (Cantor et al., 2012). None of these studies specifically addresses diagnostic accuracy and prehospital triage decisions in patients with presumed STEMI in the context of cardiac arrest. False-positive activations of primary angioplasty facilities reportedly range between 20-31% (Davis, Fisher, et al., 2007; Swan, Nighswonger, Boswell, & Stratton, 2009; Rokos et al., 2010; Young et al., 2011) although there is acknowledgement that a level of false positive activation is inevitable in maintaining an appropriate level of sensitivity in the emergency setting (Smith, 2001; Pilbery, Teare, Goodacre, & Morris, 2016). One North American study found higher false positive activations resulting from emergency department versus EMS referral, suggesting that EMS providers are capable of determining which patients are appropriate for HAC admission at a level at least comparable with ED clinicians in some systems (Lu et al., 2016).

7.19 ECG findings and angiography.

Significant differences in clinical and demographic characteristics were observed in patients undergoing angiography versus those not exposed to this procedure. Median age was significantly

lower in patients undergoing angiography (64 versus 78 years, p<.001) and higher proportions of patients who presented in a shockable versus non-shockable rhythm underwent angiography (86.7% versus 47.2%, p<.001). Given that these variables are established predictors of survival (Sasson et al., 2010) there is considerable potential for selection bias towards patients likely to achieve more favourable clinical outcomes where decisions relating to angiography were made in participating HACs. Existing inclusion and exclusion criteria for angiography post ROSC vary between studies internationally (Radsel & Noc, 2013). The presence of an extra-cardiac cause of arrest or significant comorbidities with low likelihood of favourable neurological outcome are common exclusion criteria (Sideris et al., 2011; Zanuttini et al., 2013; Garcia-Tejada et al., 2014). Institutional indications for angiography range from all patients with presumed cardiac aetiology regardless of ECG findings (Sideris et al., 2011) to all those with ST elevation and on a case-by-case basis for other ECG patterns (Zanuttini et al., 2013), to a case-by-case approach in all patients (Garcia-Tejada et al., 2014). Timing of ECG interpretation also varies from the first prehospital ECG (Sideris et al., 2011) to the first ECG obtained after hospital arrival (Garcia-Tejada et al., 2014). In the current study, ECG diagnosis was based on ambulance clinician interpretation of the prehospital ECG and no assessment of diagnostic accuracy was undertaken. A study of prehospital versus hospital ECG assessment in a physician EMS system identified comparable diagnostic utility of ECGs acquired in both settings (Muller, Schnitzer, Brandt, & Arntz, 2008), however the administration of adrenaline (Struthers, Reid, Whitesmith, & Rodger, 1983) and reperfusion injury (Adrie et al., 2002) have both been associated with ECG changes which may affect diagnosis and clinical decision making especially in the early stages post ROSC (Dumas et al., 2016).

In the current study, more than a quarter of patients (n=46, 26.3%) with ST elevation and more than a third of those with ST depression (n=7, 36.8%) did not undergo angiography. These trends are broadly comparable with existing evidence examining the value of 12 lead ECG findings in predicting the presence of acute coronary lesions. A retrospective review of adult out-of-hospital cardiac arrest survivors who underwent angiography in an Italian centre identified significant coronary lesions in 98% (n=39) of those with ST elevation and in 77% (n=39) of those with other ECG patterns. These lesions were presumed to be acute in 85% (n=34) of cases with ST elevation versus 56% (n=51) with other ECG patterns (p<.001) (Zanuttini et al., 2013). Similarly, Garcia-Tejada et al. found that acute coronary lesions were more common in patients with ST elevation than other ECG patterns (83% versus 8%, p<.001) (Garcia-Tejada et al., 2014). Sideris and colleagues identified that physician recognition of ST elevation on the prehospital ECG in a French EMS system predicted acute myocardial infarction with 88% sensitivity and 84% specificity. Broadening this to include patients with ST depression yielded a sensitivity of 95% and specificity of 62%, whereas combined criteria of

ST depression or elevation and any widened QRS or left bundle branch block resulted in sensitivity of 100% and specificity of 46% (Sideris et al., 2011). It is therefore likely that the variation in rates of angiography according to ECG findings observed in the current study is a reflection of in-hospital decisions relating to the likelihood of an acute coronary lesion requiring primary intervention versus the risk and resource implications associated with emergent angiography.

7.20 Angiography and primary percutaneous coronary intervention

A significantly higher proportion of patients with good versus poor neurological outcomes underwent angiography in the HAC. Patients undergoing angiography were more likely to be male, have presented in a shockable rhythm and to be treated with mild therapeutic hypothermia as part of subsequent in-hospital management. Median age was also significantly lower in patients exposed to angiography. These findings are consistent with previous research within the same EMS system across all receiving HAC hospitals (Fothergill et al., 2014) which identified that the proportions of younger patients, male gender, and shockable rhythm were higher in those undergoing angiography. Furthermore, the single-centre Harefield study identified that younger age and the presence of a shockable rhythm were significant predictors of survival in patients undergoing angiography (Iqbal et al., 2015). These factors are known predictors of improved outcome in the wider out-of-hospital cardiac arrest literature (Sasson et al., 2010) and therefore patients in the angiography group were arguably more likely to have improved outcomes at the outset. Although no RCT data exists relating to the influence of angiography on outcomes following resuscitation from out-of-hospital cardiac arrest, meta-analysis of observational studies suggests improved outcomes with survival ranging from 41-92% (Larsen & Ravkilde, 2012). Although considerable heterogeneity was identified, the pooled unadjusted odds of survival were significantly higher in patients treated with an early invasive strategy versus standard treatment (OR 2.78, 95% CI 1.89-4.10). More recent multivariate analysis of prospective data from a physician led EMS system found immediate successful coronary angioplasty to be an independent predictor of survival in patients with no obvious non-cardiac cause of out-of-hospital arrest regardless of post ROSC ECG findings (OR 2.06, 95% CI 1.16-3.66). However, considerable variation in protocols for post ROSC angiography, criteria for procedural selection (Radsel & Noc, 2013) and outcomes between individual HACs (Mumma et al., 2015) have also been identified, suggesting that institutional guidelines and behaviour of clinicians may be important factors in determining which patients ultimately undergo angiography.

7.21 Mild therapeutic hypothermia following hospital admission

Initiation of mild therapeutic hypothermia as part of subsequent in-hospital management was associated with improved unadjusted odds of survival with good neurological outcome (OR 1.818,

95% CI 1.137-2.909) in the current study. This is in keeping with results from earlier small scale randomised controlled trials comparing initiation of mild therapeutic hypothermia on hospital arrival versus standard care for patients presenting in shockable rhythms with ROSC following out-of-hospital cardiac arrest in Australian paramedic (Bernard et al., 2002) and European physician (Hypothermia after Cardiac Arrest Study Group, 2002) EMS systems, which demonstrated improved neurological outcomes associated with hypothermia. Subsequent trials addressing initiation of therapeutic hypothermia during the prehospital phase either intra-arrest (Debaty et al., 2014) or post ROSC (Kim, Nichol, et al., 2014) have failed to demonstrate any significant outcome benefit over treatment delayed until hospital arrival (Huang et al., 2015). Multiple neuroprotective mechanisms are thought to be associated with hypothermia, including a reduction in cerebral blood flow and oxygen consumption in the order of 7-8% per 1^{o}C temperature decrease (Rosomoff & Holaday, 1954; Milde, 1992), resulting in less metabolic demand and therefore anoxic injury (McCullough et al., 1999; Polderman, 2004). Other studies suggest that pathways responsible for apoptotic pre-programmed cell death may be attenuated via hypothermia (Yenari & Han, 2012), in addition to reduced inflammation, cerebral oedema (Jurkovich, Pitt, Curreri, & Granger, 1988; Chi, Liu, & Weiss, 2001), and harmful free radical production (Globus, Alonso, Dietrich, Busto, & Ginsberg, 1995). More recent evidence suggests that it may be prevention of hyperthermia rather than induction of hypothermia per se that is responsible for improved survival (Nielsen et al., 2013; Nielsen et al., 2014), and current guidelines recommend temperature management targeted to ≤36^{o}C rather than induction of hypothermia to achieve a temperature range of 32-34^{o}C (Nolan et al., 2015). Standard guidelines in use throughout the data collection phase of the current study advocated hospital-based induction of therapeutic hypothermia as part of standard post ROSC care (Fukuda, 2016), which may account for the relatively high proportions of patients overall who were cooled as part of in-hospital management. Equally other studies suggest that angiography and mild therapeutic hypothermia should be offered as combination therapy, and this may provide some explanation for the relatively higher proportions of cases exposed to this intervention in the angiography group (Wolfrum et al., 2008).

Once hypothermia is induced it is imperative that cooling measures are maintained within the recommended range usually for a period of at least 24-hours (Nolan et al., 2015) as fluctuations in temperature may be harmful (Merchant et al., 2006). With this in mind, it is unlikely that hospital clinicians would initiate hypothermia in cases where further treatment was regarded as futile, especially as neurological prognostication following induction of hypothermia may be unreliable (Rossetti, Oddo, Logroscino, & Kaplan, 2010). Therefore, the higher rates of hypothermia in patients undergoing angiography may similarly reflect selection bias towards those more likely to achieve

favourable neurological outcomes anyway. A significantly higher proportion of patients who presented in a shockable versus non-shockable rhythm were exposed to therapeutic hypothermia (62% versus 25%, χ^2 25.437, p<.001). This approach appears consistent with established evidence which demonstrates a clear survival benefit of hypothermia in shockable rhythms (Hypothermia after Cardiac Arrest Study Group, 2002; Bernard, Smith, et al., 2010) and guidelines in use during the data collection phase which acknowledged the less compelling nature of the evidence for hypothermia in non-shockable rhythms (Morrison et al., 2010; Kim, Yim, Jeong, Klem, & Callaway, 2012).

7.22 Influence of airway management on outcome

The overall finding that there is no significant difference in the proportion of patients with good versus poor neurological outcome according to airway management approach is perhaps unsurprising given the ongoing controversy and scientific equipoise associated with airway management in out-of-hospital cardiac arrest. Unadjusted odds ratios for all cases (OR 1.107, 95% CI 0.929-1.320) and patients who presented in a shockable rhythm (OR 1.013, 95% CI 0.738-1.392) demonstrated no significant differences in the odds of poor outcome associated with ETI versus SGA. A significant increase in the unadjusted odds of poor outcome with ETI was noted in patients presenting in a non-shockable rhythm. However, there were relatively small numbers of patients overall with good neurological outcomes in this cohort (n=5), none of whom was intubated. When adjusted for bystander CPR, witnessed arrest, presence of shockable rhythm, age and time to ROSC, the odds of poor outcome with ETI were not significant (adjusted OR 0.836, 95% CI 0.341-3.130).

Earlier studies investigating the influence of airway management on survival in out-of-hospital cardiac arrest have tended to find either no difference in outcomes between different airway management approaches (Egly et al., 2011), or a trend towards worse outcomes associated with any form of advanced airway management versus basic measures alone (Arslan Hanif et al., 2010; Studnek et al., 2010). In these studies, adjusted odds of improved outcome in patients not exposed to ETI range from 2.33 (95% CI 1.63-3.33) (Studnek et al., 2010) to 4.5 (95% CI 2.3-8.9) (Arslan Hanif et al., 2010). Multivariate analysis by Egly et al. found that ETI significantly decreased survival to discharge in patients presenting in a shockable rhythm (adjusted OR 0.52, 95% CI 0.27-0.998) but increased survival to admission in those with non-shockable rhythms (adjusted OR 2.94, 95% CI 1.16-7.44) (Egly et al., 2011). These trends contrast with those from the current study, which identified increased unadjusted odds of poor outcome associated with ETI versus SGA in non-shockable rhythms and no significant difference in outcome for patients presenting in a shockable rhythm or following multivariate analysis.

As discussed previously, variation in systems and procedures and the retrospective observational nature of these studies renders meaningful comparison challenging, particularly when the current study is focussed upon examining outcomes solely in a specific sub-set of patients with ROSC complicated by STEMI. The inability to control for time to ROSC in many retrospective studies is a major limiting factor, given that shorter time to ROSC is associated with improved outcomes and a reduced requirement for advanced airway management. Data relating to both time to ROSC and age were collated and identified as significant predictors of survival in the current study, enabling their incorporation as part of subsequent multivariate analyses. Missing data may also compromise results, with Arslan Hanif et al. reporting missing discharge data for 16% (n=48) of patients, all of whom were categorised as having poor outcome in subsequent analyses (Arslan Hanif et al., 2010). The resuscitation populations included in these studies are also more heterogenous which contrasts with the relatively homogenous sample of post-ROSC patients with evidence of STEMI recruited for the current study. Data collection for these studies also occurred prior to important revisions in international resuscitation guidelines, which refocussed attention on the provision of high quality chest compressions and de-emphasised advanced airway management, particularly where this might result in interruptions to compressions (Ewy, 2009).

Two more recent large-scale prospective registry analyses of outcomes in cardiac arrest have both identified small but statistically significantly improved odds of good neurological outcome associated with ETI versus SGA use (Wang et al., 2012; McMullan et al., 2014). In keeping with the approach adopted in the current study, these analyses compared ETI with supraglottic airway insertion, although a wider range of supraglottic devices were in use throughout the EMS agencies participating in this research and the populations were again more heterogenous in terms of both variability in EMS system (Davis, Garberson, et al., 2007) and aetiology. Analysis of the CARES registry demonstrated that ETI achieved higher sustained ROSC (OR 1.35, 95% CI 1.19-1.54), survival to hospital admission (OR 1.36, 95% CI 1.19-1.55), hospital survival (OR 1.41, 95% CI 1.14-1.76) and hospital discharge with good neurologic outcome (OR 1.44, 95% CI 1.10-1.88) when compared with cases managed via SGA (McMullan et al., 2014). Similarly, ROC PRIMED analysis (Wang et al., 2012) found that ETI was associated with increased survival to hospital discharge (adjusted OR 1.40, 95% CI 1.04-1.89), ROSC (adjusted OR 1.78, 95% CI 1.54-2.04) and 24-hour survival (adjusted OR 1.74, 95% CI 1.49-2.04). McMullan et al. further identified that patients managed via basic airway manoeuvres alone and therefore not exposed to advanced airway management versus those undergoing ETI or SGA insertion exhibited higher adjusted odds of survival to discharge with good neurological outcome (adjusted OR 4.19, 95% CI 3.09-5.70), however time to ROSC was not incorporated in multivariate analyses. It may therefore be that airway management via basic means alone is a

marker for shorter to time ROSC which is a predictor of improved neurological outcome (Komatsu et al., 2013). In addition, much higher proportions of patients underwent ETI versus SGA insertion in both the CARES (81.2% versus 18.8%) and ROC PRIMED (52.6% versus 29.3%) studies when compared with data from the current study (27.3% versus 72.7%).

7.23 Summary

In terms of the principal research objective, the current study found no significant association between airway management approach and neurological outcome in out-of-hospital cardiac arrest patients who achieved ROSC and underwent direct transfer to a HAC. The study sample represents a unique sub-set of out-of-hospital resuscitation patients in whom no previous airway management research has been undertaken, however this may render comparisons with other studies problematic. In the current study dataset, certain variables established as predictors of survival in the wider resuscitation literature, such as witnessed arrest, bystander CPR and response times, were not significantly associated with improved outcomes. This may reflect the relatively homogenous nature of the study sample and the choice of ROSC as part of inclusion criteria. Conversely, other variables not routinely recorded in several previous studies, such as shorter time to ROSC and median $ETCO_2$, were noted to have a significant influence on outcome. These results support the inclusion of these variables as part of the dataset, and provide useful information regarding potential confounding factors for future observational airway management and cardiac arrest research. The following chapter considers the overall strengths and limitations of the study, including internal and external validity of findings.

8. Strengths and Limitations

8.1 Introduction

In this chapter, the strengths and limitations of the programme of research are reviewed. The influence of study inclusion and exclusion criteria, diagnostic accuracy, and patient selection by paramedics in relation to sample demographics are discussed. The potential for confounding factors such as variation in clinical skills, scope of practice and practitioner behaviours to bias study results is acknowledged. Consideration is given throughout to internal and external validity, particularly in relation to the generalisability of results to other resuscitation populations and EMS systems. Specific strengths of this research are highlighted, acknowledging the extent to which these are in part attributable to learning from preceding literature review and a breadth of knowledge of previous studies and methodological approaches. The unique contribution of the study findings in the context of the growing body of research addressing out-of-hospital airway management is also emphasised.

8.2 Study inclusion and exclusion criteria

External validity reflects the extent to which study results are generalizable and can be applied to a wider population (Peat, 2002). The inclusion and exclusion criteria developed for the current study ensured that only patients who achieved ROSC after resuscitation incorporating advanced airway management and met the criteria for transfer to a HAC were eligible for enrolment. These criteria were necessarily narrow in order to capture the specific resuscitation population of interest and to permit investigation of an area of practice where there is currently a paucity of evidence. A number of other observational studies addressing airway management in cardiac arrest have recruited patients with a range of aetiologies (Wang et al., 2012; McMullan et al., 2014), leading to difficulties in performing multivariate analysis and introducing a significant element of confounding (Petrie & Sabin, 2009). The current study sample provides a greater degree of clinical homogeneity, potentially enhancing the validity of comparisons between different airway management approaches due to a common presumed aetiology. Performing research within a well-established network of HACs involving a single EMS provider also resulted in a low level of participants lost to follow up and facilitated access to hospital records.

However, it is important to acknowledge that this approach will have led to the exclusion of both patients in whom resuscitation attempts were unsuccessful and those who achieved sufficiently prompt ROSC that active airway management and ventilation were not required, such as an episode of witnessed VF with immediate defibrillation and successful cardioversion. The a priori exclusion of patients exposed to out-of-hospital resuscitation attempts who did not achieve ROSC is an important

limiting factor as this precludes use of study data to determine the mortality effects of different airway management approaches in the wider resuscitation population. There is currently significant scientific equipoise in this area, with some studies suggesting no difference in outcome according to the airway management approach employed (Egly et al., 2011) versus those identifying significantly improved outcomes (Wang et al., 2012; McMullan et al., 2014) or increased mortality (Arslan Hanif et al., 2010; Studnek et al., 2010) associated with endotracheal intubation in cardiac arrest. Results from the current study cannot contribute to this debate as no assessment of airway management approach in patients where resuscitation was terminated in the field or the patient was transported intra-arrest to an ED rather than a HAC was undertaken.

8.3 Prehospital diagnostic accuracy and patient selection

The criteria for admission to a HAC post ROSC in the current study are clearly defined in standard guidelines issued by the host EMS service (Fothergill et al., 2014). In this setting, paramedics and other ambulance clinicians make autonomous decisions to transfer patients directly to HACs able to receive them at any time of the day or night. Although standard criteria define which patients are eligible for HAC admission, the post ROSC ECG is interpreted by the lead ambulance clinician without recourse to a physician or other clinical support. This approach contrasts with some paramedic systems where there is a requirement to transmit the ECG for remote interpretation and authorisation to proceed (Ting et al., 2008; Werman, Newland, & Cotton, 2011; Bosson et al., 2015) and physician led EMS systems where admission criteria are less standardised or broader and there is more latitude for decisions on a case-by-case basis (Dumas et al., 2010; Geri, Dumas, & Cariou, 2014; Dumas et al., 2016). Although the standardised criteria applied in the current study enables the study sample to be clearly defined, the extent to which these findings may be generalised to other EMS systems employing different clinical decision-making approaches is debatable.

Accuracy of ECG diagnosis and adherence to admission criteria were not assessed as part of the current study. Although diagnostic accuracy of UK paramedics has previously been shown to be relatively high in diagnosing the presence of ST elevation (Whitbread et al., 2002), it is possible that some patients transferred directly to participating HACs did not fulfil the ECG or clinical criteria as stipulated. Existing evidence suggests a higher incidence of acute coronary lesions requiring primary intervention in patients undergoing angiography in the presence of ST elevation versus other ECG patterns potentially indicative of acute coronary syndrome (Zanuttini et al., 2013; Garcia-Tejada et al., 2014). In the current study, there is therefore the potential for unidentified non-adherence to guidelines for HAC admission to confound results by increasing the proportion of non-ST elevation presentations in a given group.

8.4 Distribution of airway management interventions

The proportion of patients in whom endotracheal intubation was performed is considerably lower than that seen in studies from comparable EMS systems (Arslan Hanif, Kaji, & Niemann, 2010; Egly et al.., 2011; McMullan et al.., 2014; Wang et al.., 2012). Indeed the host EMS service remains at present unique within the UK in permitting only certain paramedics to continue to practise the skill of intubation (Gregory, Kilner, & Arnold-Jones, 2015). Ultimately the airway management approach employed is at the discretion of the ambulance clinician within the constraints of their clinical scope of practice and national clinical guidelines. Although it is not possible to predict what effect an increase in the proportion of patients undergoing ETI would have had, any comparisons with other EMS systems where paramedics capable of intubation routinely attend all cardiac arrests and patient exposure to this procedure is higher should be made with caution.

8.5 Outcome measures

The low response rate to requests for participation in telephone administration of the SF-36 survey amongst survivors judged to have a good neurological outcome resulted in inadequate data for further statistical analysis and reliance solely on CPC results for subsequent assessment of outcome. Although the CPC scale was not originally designed for use in cardiac arrest research (Jennett & Bond, 1975), it has been described as the standard outcome measure in this domain (Raina et al., 2008). It also remains the most commonly used instrument to measure outcome in cardiac arrest (Whitehead et al., 2015), capable of providing a reasonable assessment of broad functional outcome category (Hsu et al., 2014). This provides a degree of reassurance regarding the face validity of the CPC as measure of outcome in the current study. Whilst the ability to determine CPC classification via retrospective review of clinical notes is attractive in the context of cardiac arrest research, the limitations associated with this approach including the accuracy, legibility and completeness of relevant documentation renders CPC data liable to misclassification bias (Peat, 2002). Although concerns have been raised regarding inter-rater reliability where multiple researchers assess CPC (Hsu et al., 1996), the use of a single researcher to determine CPC in the current study serves to strengthen reliability.

It has been suggested that CPC may overestimate the potential for good long term cognitive and disability outcomes, especially when compared with more sophisticated quality of life measures (Rittenberger et al., 2011). The failure to obtain adequate data relating to post discharge functional status via the pre-planned administration of the SF-36 survey therefore remains a major limiting factor in determining the potential influence of airway management approach on long term functional and cognitive status of survivors. Results from the limited SF-36 data demonstrate

individual mental and physical health component scores that are frequently above population norms, suggesting a significant likelihood of response bias in favour of survivors with better cognitive and functional status.

8.6 Practitioner level factors – experience and clinical scope of practice

Practitioner level factors such as level of training, previous exposure to cardiac arrest, procedural competence and experience, and number of rescuers present at a resuscitation attempt are potentially significant confounding factors which were not controlled for in the current study (Dyson, Bray, Smith, Bernard, & Finn, 2014). Although it was possible to determine the number of vehicles responding to each case, it was not possible to reliably determine the level of involvement of individual practitioners in clinical management. Relevant human resources and training records within the host ambulance service were not sufficiently sophisticated to quantify cumulative exposure to cardiac arrest or procedural experience with specific clinical interventions. During the study period an additional tier of advanced paramedic practitioners became operational and attended a small number of cardiac arrests, however the volume of cases attended was insufficient to determine any significant clinical effects.

The Ontario Prehospital Advanced Life Support study reported no survival benefit from the incremental addition of advanced life support skills to all practitioners within an EMS system already optimised to achieve rapid defibrillation (Stiell et al., 2004). However, a retrospective review of cardiac arrests in the Queensland region of Australia identified that augmentation of a standard paramedic response by an additional tier of more highly trained and experienced intensive care paramedics (ICP) resulted in significantly higher survival in the ICP group after adjustment for factors known to influence survival (Woodall, McCarthy, Johnston, Tippett, & Bonham, 2007). Nishi et al. found that the presence of multiple professional rescuers at out-of-hospital cardiac arrests in Japan was independently associated with increased one year survival, although this was not significant for cases occurring in the home environment (Nishi et al., 2013). A retrospective cohort study of witnessed out-of-hospital VF cardiac arrests in North America found that for every additional year of experience of the lead paramedic responsible for performing invasive procedures such as endotracheal intubation and intravenous access, likelihood of survival increased by 2% (95% CI 1.00-1.04), although the level of experience of the paramedic leading the resuscitation attempt did not influence survival (OR 1.01, 95% CI 0.99-1.03) (Gold & Eisenberg, 2009). Overall odds of survival increased by 1% for every additional year of paramedic experience (95% CI 1.00-1.03). Similarly, multivariate analysis of all cardiac arrest cases in which resuscitation was attempted in the Victoria region of Australia identified that when compared with practitioners with less than 6 resuscitation

attempts in the preceding three years, odds of survival increased incrementally where median exposure to resuscitation was 7-11 (adjusted OR 1.26, 95% CI 1.04-1.54), 12-17 (adjusted OR 1.29, 95% CI 1.04-1.59) and >17 (adjusted OR 1.5, 95% CI 1.22-1.86). Increased exposure of paramedics to cases of cardiac arrest was also associated with reduced odds of initiating resuscitation where this was felt to be futile ($p < .001$). Years of experience as a paramedic per se was not associated with improved survival (Dyson et al., 2016). These results suggest that practitioner exposure and clinical scope of practice may be important factors in survival which were not controlled for in the current study. However, when assessing the influence of practitioner experience and exposure to cardiac arrest on outcomes, it is important to be cognisant of appreciable differences in EMS systems within North America (Gold & Eisenberg, 2009) and Australia (Dyson et al., 2016) where the response to out-of-hospital cardiac arrest frequently includes an additional tier of more highly trained and experienced paramedics (Trevithick et al., 2003; Pozner et al., 2004). In these settings, the initial response to cardiac arrest may be provided by individuals with comparatively less training than that provided to UK paramedics (Black & Davies, 2005), including firefighters restricted to automated defibrillation and basic life support prior to the arrival of more highly skilled rescuers in some services (Kwok et al., 2013). In contrast, the UK ambulance service response typically incorporates paramedics operating within a standard scope of practice to all cardiac arrests (Black & Davies, 2005) and therefore results from the current study are reflective of the UK practice setting.

8.7 Practitioner attitudes and behaviours

Practitioner attitudes and behaviours have been acknowledged as highly influential factors in previous prehospital research programmes (Pocock et al., 2016), and were specifically highlighted in relation to treatment and transfer decisions and thus the study randomisation process in the context of the recent Australian Head Injury Retrieval Trial (Garner, Mann, Fearnside, Poynter, & Gebski, 2015). The availability of supraglottic and extraglottic airway devices as an alternative to endotracheal intubation may also affect practitioner behaviour. Early research within a North American EMS system reported a significant reduction in intubation success rates following the introduction of the Combitube extraglottic device (93.5% versus 91.6%, $p=.007$) (Cady & Pirrallo, 2005). More recent data identified that the introduction of the King Laryngeal Tube resulted in a significant reduction in the proportion of patients undergoing endotracheal intubation (72.3% versus 67.1%, $p=.007$) but no significant reduction in the odds of successful intubation (OR 1.02, 95% CI 0.74-1.41) (Hilton, Wayne, & Martin-Gill, 2016). Whilst this may be influenced by the clinical utility of specific alternative extraglottic devices available within each system, these results suggest that the availability of an alternative airway device may influence practitioner behaviours and therefore patterns of airway management approaches within individual EMS systems.

A recent audit identified that despite calls to de-emphasise the role of endotracheal intubation by UK paramedics in cardiac arrest (Deakin, Clarke, et al., 2010), the majority of UK ambulance services with the exception of the host EMS service permit all paramedics to perform endotracheal intubation, although supraglottic devices are universally available (Gregory et al., 2015). Although it was not possible to determine whether an intubation-trained paramedic was present at the scene in the current study, the potential for practitioners to utilise a potentially less technically demanding intervention such as SGA insertion in patients where airway challenges were anticipated and therefore introduce a degree of selection bias cannot be ignored. Conversely, there may have been cases where the attending ambulance clinicians would have selected ETI as the preferred technique had this procedure been available to them at the time. On the basis of the national airway audit results reported above (Gregory et al., 2015), this is not a situation that would arise in any other UK ambulance service and therefore this may further limit the generalisability of these results.

8.8 Prehospital timings

A major strength is that key timings were available for a number of aspects of clinical treatment and the patient journey, enabling these to be incorporated into bivariate and multivariate analyses. However, it is important to note that the accuracy with which individual timings were recorded may vary. Electronic time-based measures recorded via computer-aided dispatch systems, which include variables such as response time, on-scene time and hospital transfer times are recorded remotely. This provides a superior data collection solution in the context of out-of-hospital cardiac arrest when compared with hand-written records (Pocock et al., 2016). In contrast, timings related to clinical interventions are recorded manually by the attending ambulance clinicians. During out-of-hospital resuscitation, life-saving interventions must be prioritised over recording of data (Lyon, Egan, et al., 2010), therefore the potential for inaccuracies in times recorded for interventions such as SGA insertion, ETI, administration of drugs or time to ROSC cannot be ignored. Nonetheless, in keeping with other studies (Komatsu et al., 2013) shorter time to ROSC was found to be a significant predictor of outcome, yet this is rarely known or incorporated into multivariate analysis in a number of other observational airway studies (Arslan Hanif et al., 2010; Studnek et al., 2010; Nagao et al., 2012; Tanabe et al., 2013). The time taken to achieve ROSC may dictate whether airway management escalates to advanced techniques, potentially leading to erroneous assumptions regarding the negative effect of advanced airway management on outcomes. Individual response times, time to advanced airway placement and transfer time to HAC were also available. These timings are not consistently incorporated as part of observational data in other studies (McMullan et al., 2014), yet may have a significant bearing on clinical outcomes.

8.9 Prehospital clinical dataset

The breadth of clinical variables for which data were collected is also a strength of the study when compared with other observational research. In contrast with a number of similar studies, physiological data relating to prehospital $ETCO_2$, temperature, capillary blood glucose, systolic blood pressure, and failed intubation attempts were routinely available. $ETCO_2$ values have been demonstrated to correlate with outcome in cardiac arrest (Kolar et al., 2008), with levels below a given threshold often used to guide decisions relating to the viability of resuscitation attempts. Prehospital temperature is rarely incorporated as a standard measure in resuscitation research, yet the presence of fever is a predictor of worsened outcome post ROSC (Langhelle et al., 2003). Similarly, raised blood glucose is often not reported in cardiac arrest research but is associated with worsened outcomes post admission (Nolan et al., 2007). The presence of cardiogenic shock as indicated by hypotension is a longstanding predictor of worsened outcome (Bray et al., 2014), yet data relating to prehospital blood pressure is rarely available or recorded during the course of airway management research. Finally, failed attempts at intubation may result in significant interruptions to chest compressions and prolonged periods of hypoxia (Wang, Lave, Sirio, & Yealy, 2006). This may lead to use of the SGA primarily as a rescue device, thus potentially representing a marker for worsened outcomes rather than an inherently harmful intervention. Despite this, several studies comparing ETI and SGA do not include data on the number of occasions where the SGA was used after failed attempts at intubation. Accounting for confounding factors is an important aspect of observational research, particularly when regression analysis is undertaken (Woodward, 2014). The availability of prehospital data for a number of outcome predictor variables not routinely collected in other research is therefore a particular strength of the current study.

8.10 Summary

The limitations outlined above are generally consistent with those conventionally associated with observational research, where patients cannot be randomised to different treatment arms (Peat, 2002). As discussed previously, the fact that not all practitioners within the host EMS system perform ETI meant that randomisation would have been difficult to achieve, even if the very significant resources required to achieve this had been available. One inevitable consequence of this is that practitioner level factors could not be controlled for. Unlike North American systems (Pozner et al., 2004), where an appreciable proportion of airway management research has been conducted , UK paramedics are not routinely subject to on-line medical control, and practise via guidelines rather than protocols (Black & Davies, 2005) which may have resulted in more variation in clinical management. Conversely, a number of studies utilise data contributed from multiple services (Wang et al., 2012; McMullan et al., 2014) whereas the current study was conducted within a single

service with a single standardised guideline for resuscitation (Fothergill et al., 2014). Many of the strengths discussed above reflect learning from the literature review phase of the research programme. This provided an opportunity to identify missing variables highlighted in prior studies conducted in a range of EMS systems and ensure that these were addressed within the current study dataset wherever possible. The very significant role of shorter time to ROSC in predicting outcomes is a clear example of this, and serves to highlight the particular strengths of the current study in obtaining key prehospital timings not consistently recorded in other research.

9. Conclusion

9.1 Introduction

The final chapter returns to the primary research question, summarising the overall results, identifying the unique contribution made by the programme of research, and reflecting upon the implications for current and future practice. A critique of both national and international randomised controlled trials currently underway addressing airway management in out-of-hospital cardiac arrest is offered and the potential contribution of and pitfalls associated with these are considered from both clinical and professional perspectives. Recommendations for future research are made, based on both evidence gaps identified during literature review and the findings of the current study.

9.2 Returning to the research question

The current study found no significant difference in outcomes between management via endotracheal intubation versus supraglottic device in patients transferred directly to a HAC following ROSC after out-of-hospital cardiac arrest. This is consistent with results from several existing studies drawn from more heterogenous resuscitation populations but contrasts with others suggesting improved outcomes associated with ETI versus SGA. No previous studies examining the influence of airway management in cases transferred directly to a HAC post ROSC exist, and therefore these results offer a unique contribution to cardiac arrest research in this subset of patients. These results also provide a degree of reassurance to the participating EMS system regarding non-inferiority of endotracheal intubation when compared with supraglottic airway use. Results from the SF-36 health survey administration phase of the study highlight the challenges associated with achieving an adequate response rate in cardiac arrest research where attempts are made to provide more sophisticated measures of functional outcome in survivors. Nonetheless, evidence from the limited pool of patients from which SF-36 results were obtained suggests that at least some survivors of cardiac arrest subsequently experience physical and mental health that is comparable with or exceeds population norms. As both outcome measurement and clinical management strategies evolve, future efforts should be targeted towards not only improving survival but also increasing the proportion of those surviving with both physical and mental health that is at least comparable with population norms.

In terms of secondary objectives, the breadth of data collected from the prehospital phase of care were sufficient to permit investigation of clinical and demographic variables influencing outcomes,

and to compare these characteristics according to the airway management approach employed. Some of these variables, notably time to ROSC, are highly influential in terms of clinical outcomes but rarely incorporated as part of data collection in other studies investigating airway management in cardiac arrest. Other variables recorded during the post ROSC phase such as temperature, presence of hypotension, blood glucose, and drug therapy are not routinely reported by the host EMS system (Fothergill et al., 2013; Fothergill et al., 2014). These data enhance understanding of the post ROSC phase of care and also provide information to guide and inform future developments in out-of-hospital resuscitation. For example, the majority of patients did not experience fever or hyperglycaemia, therefore it is unlikely that further interventions are required in these areas during the prehospital phase of care. Conversely, an episode of hypotension or the administration of adrenaline in the post ROSC phase were significantly associated with worsened outcome, therefore the host EMS system may need to consider further strategies to optimise blood pressure prior to transfer to a HAC.

9.3 Future direction

Adjustment for confounding is an issue in all forms of observational research (Peat & Barton, 2014; Woodward, 2014) and constitutes an appreciable challenge in the context of out-of-hospital cardiac arrest. The relatively uncontrolled and sometimes chaotic prehospital environment coupled with variation in numbers and skill levels of attending EMS providers present unique challenges for researchers which are not present to the same extent in more predictable clinical environments (Lyon, Egan, et al., 2010). Given the limitations of observational studies, the overriding aim for future researchers must therefore be to conduct appropriately powered well-designed prehospital randomised controlled trials to provide more definitive evidence relating to the optimal airway management strategy in out-of-hospital cardiac arrest. Within the UK, the feasibility of conducting a randomised albeit underpowered trial relating to out-of-hospital airway management has been demonstrated (Benger et al., 2013), and an appropriately powered multi-site RCT is now underway. The primary aim of the AIRWAYS-2 trial is to determine whether management via the i-gel supraglottic device in adult non-traumatic out-of-hospital cardiac arrest is superior to endotracheal intubation. Modified Rankin Scale will be assessed in survivors at three and six months, with outcomes compared between the airway management groups. Cluster randomisation techniques will assign individual paramedics to either the supraglottic airway or endotracheal intubation arms of the study. Data analysis will be conducted on an intention-to-treat basis with a target sample of 9,070 patients recruited by 1,300 paramedics over a two-year period (Taylor et al., 2016). Recruitment has also commenced for a similar trial employing cluster randomisation techniques in North America under the auspices of the Resuscitation Outcomes Consortium (ROC). The Pragmatic

Airway Resuscitation Trial (PART) will compare the effectiveness of endotracheal intubation versus laryngeal tube insertion in adult non-traumatic out-of-hospital cardiac arrest. In contrast with AIRWAYS-2, PART employs crossover randomisation whereby EMS agencies participating in the study alternate between the two trial arms every three to six months. In addition, PART is only powered to detect 72-hour survival and therefore has a smaller target sample size (n=3,000) (Wang et al., 2016).

However, models of EMS provision (Davis, Garberson, et al., 2007) and professional background, level of training, exposure and experience of EMS responders can profoundly influence out-of-hospital cardiac arrest outcomes (Clarke, Lyon, Short, Crookston, & Clegg, 2014; Dyson et al., 2014; Bottiger, Bernhard, Knapp, & Nagele, 2016; Dyson et al., 2016) and vary globally (Lockey, 2009). Furthermore, such characteristics demonstrably affect both the range of airway management strategies available and associated procedural success rates (Davis, Hoyt, et al., 2003; Bernard, Nguyen, et al., 2010; Kwok et al., 2013; Bernard et al., 2014). Whilst the evidence relating to the influence of airway management on cardiac arrest outcomes remains equivocal, clear evidence exists that both procedural success rates and clinical outcomes in prehospital airway management are profoundly influenced by EMS operating model and provider education and exposure (Davis, Fakhry, et al., 2007).

Although more diverse and clinically sophisticated models of EMS provision within the UK are emerging (Mackenzie et al., 2009; Hughes, 2011), the general trend within UK ambulance services is to deploy a standard paramedic response to high acuity calls (Black & Davies, 2005). This contrasts with the tiered system observed in other countries where higher acuity calls receive a BLS or standard paramedic response augmented by more senior clinicians with an expanded scope of practice (Trevithick et al., 2003; Adnet & Lapostolle, 2004). Such systems frequently restrict advanced airway procedures to smaller cohorts of providers with enhanced education and higher levels of exposure, whereas in the UK predominantly the same scope of practice is available to all paramedics (Jacobs & Grabinsky, 2014). In view of this, a major concern in relation to the ongoing UK Airways 2 trial is that participating paramedics may in fact become less skilled in endotracheal intubation due to a reduction in the frequency with which the procedure is undertaken, with the result that when an endotracheal intubation attempt is required the individual provider and other ambulance clinicians providing assistance may have had less recent exposure to the technique than would have been the case prior to commencement of the trial. Although data analysis is planned on an intention-to-treat basis (Taylor et al., 2016), the risk is that AIRWAYS-2 may compare suboptimal intubation with supraglottic airway insertion, whereas a more clinically appropriate trial might

compare intubation where conditions are optimised with supraglottic airway insertion. Although the use of crossover randomisation in PART may ameliorate these issues to some extent, the same concerns will still apply. Additional research may therefore be required to define the models of EMS best suited to optimising out-of-hospital airway management. The forthcoming results of these studies will require close and careful consideration before acceptance as the basis for future airway management strategies in out-of-hospital cardiac arrest, with recommendations for further research made where appropriate.

9.4 Final summary and reflections

Cardiac arrest is a time sensitive medical emergency which requires prompt and appropriate treatment if survival is to be maximised (Perkins et al., 2015). Unlike the hospital setting where it is frequently preceded by noticeable physiological deterioration (Soar et al., 2013), out-of-hospital cardiac arrest often occurs without warning and therefore treatment cannot be deferred until admission to hospital (Deakin et al., 2015). It is only through improving the evidence base for and optimising out-of-hospital interventions that outcomes may be improved (Perkins et al., 2016). In the UK setting, this responsibility predominantly lies with NHS Ambulance Services staffed by paramedics and other ambulance clinicians (Black & Davies, 2005). Out-of-hospital cardiac arrest research presents unique challenges not routinely present in other areas of research (Lyon, Egan, et al., 2010), however these can be overcome and should not preclude high quality clinical trials (Pocock et al., 2016). Whilst randomised controlled trials represent the most robust method of determining the comparative effectiveness of a given airway management approach or technique, there remains a role for well-designed observational studies.

The primary finding that there was no significant difference between airway management groups serves to reaffirm current approaches to airway management within the host EMS service. This suggests that there is no immediate need for withdrawal of specific airway management interventions at present in the absence of any other data to the contrary. Data relating to secondary outcome measures provide a unique contribution to enhancing understanding of factors influencing survival in out-of-hospital cardiac arrest patients who undergo direct transfer to HAC facilities post ROSC, providing a basis for further quality improvement. These results demonstrate that paramedic-led out-of-hospital clinical research is both feasible and capable of providing uniquely insightful findings that may be used to guide and influence future clinical and professional development. This form of practitioner enquiry is particularly relevant in the context of global EMS systems employing a range of operational models supported by differing configurations of practitioners working in a variety of medico-legal contexts and where airway research is largely physician-led and reportedly

subject to significant publication bias (Hubble, Brown, et al., 2010). Further largescale randomised trials will be required to provide more definitive evidence and some are already underway in both the UK and North America. Ultimately, the findings of these studies will at least in part reflect the EMS systems in which they were conducted, and therefore must be interpreted with caution and due regard for context. Future research therefore needs not only to determine the optimal airway management approach in out-of-hospital cardiac arrest but also the most appropriate practitioner and EMS system configuration to achieve this. There is ample evidence that appropriately educated and experienced paramedics operating in services underpinned by robust clinical governance and targeted dispatch systems can provide high quality advanced airway management in out-of-hospital cardiac arrest.

10. References

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11. Appendices

Appendix 1 Participant information

AMICABLE Study
Airway Management in Cardiac Arrest – Basic, Laryngeal mask airway, Endotracheal Intubation

Participant Information Sheet. Version 1.3. (6/3/13)

Information about the research

You are being sent this information because you were recently treated by the London Ambulance Service NHS Trust after suffering a cardiac arrest. This is a condition where the heart stops beating. After treatment by the ambulance service, you were taken directly to a specialist Heart Attack Centre. During resuscitation, you were treated with specific techniques and devices to open your airway and assist with breathing. The London Ambulance Service and London Heart Attack Centres are taking part in a study to investigate what effect different airway techniques and devices may have on outcomes in cases like yours. It is hoped that the information from this study will help improve future approaches to treatment.

What is the purpose of the study ?

During your treatment, the London Ambulance Service staff diagnosed that you had suffered a specific form of heart attack known as an ST Elevation Myocardial Infarction (STEMI), and therefore transported you directly to a specialist Heart Attack Centre. In this form of heart attack, a clot blocks a coronary artery, depriving the heart of oxygenated blood. Hospital specialists within Heart Attack Centres are now able to perform a procedure to attempt to reopen the blocked coronary artery in patients who have suffered cardiac arrest. However, during out-of-hospital treatment and transfer to the specialist centre, it is the responsibility of London Ambulance Service staff to provide initial resuscitation and on-going treatment, including the use of a range of devices and techniques for maintaining a clear airway and assisting breathing. At present, it is not known what effect of the type of airway device may have on outcomes in patients who are transferred directly to Heart Attack Centres

What is being tested ?

The study will collect data about patients and their clinical care, including the type of airway device/s used and clinical measures such as heart rate and blood pressure. Patients who consent will participate in a health survey (SF-36) designed to assess general health and well-being approximately thirty days after the cardiac arrest occurred. Results from the health survey will be used to calculate an overall health and well-being score. Scores from individual patients will be used as part of the data analysis process to compare outcomes according to the type of airway management approach used. Clinical data will be used to investigate whether there is any difference in measures such as blood pressure or heart rate according to the airway device used. Clinical and patient information will also be used as part of statistical analysis to account for differences between patients in factors already known to influence survival, such as whether any resuscitation was provided prior to the

arrival of the ambulance service. This will allow us to look at the differences between patients treated with different types of airway device.

Am I eligible to take part in the study ?

You are eligible to take part if have suffered an out-of-hospital cardiac arrest requiring resuscitation by the London Ambulance Service and met the criteria for direct transfer to a regional Heart Attack Centre.

What exactly will I have to do ?

As you have already received hospital and ambulance service treatment, you will initially be asked to consent to the use of existing clinical records generated as a result of your cardiac arrest. If you consent to participate in the study, you will be asked to complete the SF-36 Health Survey. This survey may be administered by telephone at a mutually convenient time, and will take approximately thirty minutes. The survey will ask you to rate your physical and emotional health in relation to daily tasks such as washing and dressing and other activities such as walking or interactions with friends and relatives. After this, no further involvement is required.

What happens with my answers ?

Your answers will be anonymised, so that individual patients are not identified during data analysis. Your clinical information and results from the health survey will be used to perform statistical tests to investigate the effect of the type of airway device on outcomes in cases like yours.

How will any data or information I provide be used ?

The results will be used to help inform future approaches to resuscitation for the specific group of patients who undergo resuscitation by the ambulance service and meet the criteria for direct transfer to a regional Heart Attack Centre. It may demonstrate that a particular airway management device improves outcomes, or it may show that there is no difference between the different devices.

Will my participation be kept confidential ?

Any information collected during the study will be kept strictly confidential and will only be seen by authorised staff involved in the study and people from regulatory bodies who ensure that such studies are properly conducted. All such individuals have a duty of confidentiality to you as a research participant. Information used in the study will include only that which is necessary for the study and will be taken from your ambulance service and heart attack centre clinical records. All information will be kept in a secure location within the London Ambulance Service NHS Trust Clinical Audit and Research Unit. Your contact details (name, address etc) will only be used to maintain contact with you. It will not form part of the statistical analysis process and it will not be passed to anyone else. The data from this

study will be kept for at least seven years, after which it will be destroyed in accordance with NHS procedures.

What are the potential risks associated with participation ?

Some patients who have experienced cardiac arrest may experience distress when discussing the effects of the event on their lives. It is common for any individual who has experienced a traumatic event to experience some degree of emotional upset, and in most cases these feelings will resolve over time.

It is important to recognise that your participation in this study is entirely voluntary and you are free to withdraw at any stage. In the event that you experience any distress, the researcher will advise that you contact your General Practitioner. If you feel unable to do this, the researcher may initiate a referral on your behalf with your consent. If these symptoms emerge while completing the telephone questionnaire, you will be offered the opportunity to terminate the interview and to withdraw from the study

What happens if I decide to withdraw from the study ?

You are free to withdraw at any time without giving reasons, and your decision will be respected by the researcher.

Who is organising the study ?

The study is being organised by Tim Edwards (Paramedic Team Leader - London Ambulance Service and Senior Lecturer - University of Hertfordshire) as part of a research doctorate (PhD).

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If you are prepared to take part in the study, please complete the enclosed consent form and return it in the envelope provided

Appendix 2 Example Heart Attack Centre consultant letter

Royal Brompton & Harefield NHS
NHS Trust

Dear Patient,

Re: AMICABLE (Airway Management in Cardiac Arrest – Basic, Laryngeal Mask Airway, Endotracheal Intubation) Study

The above study is being conducted to investigate the influence of airway management approaches on clinical outcome in individuals who are transferred directly to our Heart Attack Centre after resuscitation by the ambulance service. The study is being overseen by Mr Tim Edwards, who is a London Ambulance Service Paramedic and PhD student researcher. Our department is collaborating with the London Ambulance Service, and I am aware that you may be contacted in connection with this research.

Yours faithfully

Dr Miles Dalby
Consultant Cardiologist

19th June 2013

Appendix 3 Consent form

AMICABLE STUDY
Airway Management in Cardiac Arrest – Basic, Laryngeal mask airway, Endotracheal Intubation

CONSENT FORM Version 1.2 (6/3/13)

	Initials
The purpose of this study has been explained to me	☐
I have been informed of the details of my involvement in the study	☐
My questions regarding this study have been answered to my satisfaction	☐
I understand that I am not obliged to take part in this study and may withdraw at any time without the need to justify my decision and without affecting me in any way	☐
I understand that any personal information obtained as a result of my participation in this study will be treated as confidential and will not be made publicly available	☐
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Hertfordshire, from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐

I, the undersigned, agree to take part in this study ☐

Signature of subject:.....

Name of subject:.....
(Please print)

Signature of investigator:.....

Name of investigator:.....
(Please print)

Status of investigator:.....

Date:.....

Appendix 4 Information for consultees

AMICABLE – Airway Management in Cardiac Arrest: Basic, Laryngeal mask airway, Endotracheal intubation

Information for Consultees. Version 1.3. (20/2/13)

Why am I being approached in connection with this study ?

You are being approached because you have been identified as a consultee for a patient treated by the London Ambulance Service NHS Trust after suffering a cardiac arrest. This patient meets the criteria for enrolment in the above study. A consultee is an individual who is able to consider the wishes and feelings of a person who is unable to provide consent as defined in the terms of the Mental Capacity Act 2005. At present, the condition of this person means that they are unable to provide informed consent. A consultee may be a Carer, friend or relative.

A cardiac arrest is a condition where the heart stops beating. After treatment by the ambulance service, the patient was taken directly to a specialist Heart Attack Centre. During resuscitation, the patient was treated with specific techniques and devices to open the airway and assist with breathing. The London Ambulance Service and London Heart Attack Centres are taking part in a study to investigate what effect different airway techniques and devices may have on outcomes in cases like this. It is hoped that the information from this study will help improve future approaches to treatment. We are asking you in your role as consultee to offer an opinion as to whether the person under discussion would have decided to take part in this study if they had been able to provide consent themselves.

What is the purpose of the study ?

During treatment, the London Ambulance Service staff diagnosed that the patient had suffered a specific form of heart attack known as an ST Elevation Myocardial Infarction (STEMI), and therefore transported them directly to a specialist Heart Attack Centre. In this form of heart attack, a clot blocks a coronary artery, depriving the heart of oxygenated blood. Hospital specialists within Heart Attack Centres are now able to perform a procedure to attempt to reopen the blocked coronary artery in patients who have suffered cardiac arrest. However, during out-of-hospital treatment and transfer to the specialist centre, it is the responsibility of London Ambulance Service staff to provide initial resuscitation and on-going treatment, including the use of a range of devices and techniques for maintaining a clear airway and assisting breathing. At present, it is not known what effect the type of airway device may have on outcomes in patients who are transferred directly to Heart Attack Centres.

What is being tested ?

The study will collect data about patients and their clinical care, including the type of airway device/s used and clinical measures such as heart rate and blood pressure. Clinical data will be used to investigate whether there is any difference in measures such as blood pressure or heart rate according to the airway device used. Clinical and patient information will also be used as part of statistical analysis to account for differences between patients in factors already known to influence survival, such as whether any resuscitation was provided prior to the arrival of the ambulance service. This will allow us to look at the differences between patients treated with different types of airway device.

Who is eligible to take part in the study ?

Patients are eligible to take part if they have suffered an out-of-hospital cardiac arrest requiring resuscitation by the London Ambulance Service and met the criteria for direct transfer to a regional Heart Attack Centre.

What exactly will I have to do ?

As the patient has already received hospital and ambulance service treatment, you will be asked to agree on their behalf to the use of existing clinical records generated as a result of the cardiac arrest. After this, no further involvement is required.

What happens with my answers ?

Clinical data records will be anonymised, so that individual patients are not identified during data analysis. The patients' clinical information will be used to perform statistical tests to investigate the effect of the type of airway device on outcomes in cases like this.

How will any data or information provided be used ?

The results will be used to help inform future approaches to resuscitation for the specific group of patients who undergo resuscitation by the ambulance service and meet the criteria for direct transfer to a regional Heart Attack Centre. It may demonstrate that a particular airway management device improves outcomes, or it may show that there is no difference between the different devices.

Will participation be kept confidential ?

Any information collected during the study will be kept strictly confidential and will only be seen by authorised staff involved in the study and people from regulatory bodies who ensure that such studies are properly conducted. All such individuals have a duty of confidentiality to you and to the person for whom you act as consultee. Information used in the study will include only that which is necessary for the study and will be taken from ambulance service and heart attack centre clinical records. All information will be kept in a secure location within the London Ambulance Service NHS Trust Clinical Audit and Research Unit. Your contact

details (name, address etc) and those of the individual patient will only be used to maintain contact with you. It will not form part of the statistical analysis process and it will not be passed to anyone else. The data from this study will be kept for at least seven years, after which it will be destroyed in accordance with NHS procedures.

What are the potential risks associated with participation ?

Individuals acting as consultees may experience distress when discussing the effects of the event on their lives. It is common for any individual who has experienced a traumatic event to experience some degree of emotional upset, and in most cases these feelings will resolve over time.

It is important to recognise that your participation in this study is entirely voluntary and you are free to withdraw at any stage. In the event that you experience any distress, the researcher will advise that you contact your General Practitioner. If you feel unable to do this, the researcher may initiate a referral on your behalf with your consent. You remain free at any time to withdraw the individual for whom you are acting as consultee from the study.

What happens if I decide to withdraw the patient from the study ?

You are free to withdraw the patient at any time without giving reasons, and your decision will be respected by the researcher.

Who is organising the study ?

The study is being organised by Tim Edwards (Paramedic Team Leader - London Ambulance Service and Senior Lecturer - University of Hertfordshire) as part of a research doctorate (PhD).

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Appendix 5 Health Research Authority ethical approval

NHS
Health Research Authority

NRES Committee London - Harrow
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04 February 2013 v2 re-issued

Mr Tim Edwards
Paramedic Team Leader London Ambulance Service NHS Trust
220 Waterloo Road
London
SE1 8SD

Dear Mr Edwards

Study title:	**A prospective observational study to investigate the effect of prehospital airway management strategies on mortality and morbidity of patients who experience return of spontaneous circulation post cardiac arrest and are transferred directly to Regional Heart Attack Centres by the Ambulance Service**
REC reference:	**12/LO/1911**
Protocol number:	**N/A**
IRAS project ID:	**101165**

Thank you for your letter of 28 December 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator, Libby Watson, at: nrescommittee.london-harrow@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Mental Capacity Act 2005

I confirm that the Committee has approved this research project for the purposes of the Mental Capacity Act 2005. The Committee is satisfied that the requirements of section 31 of the Act will

be met in relation to research carried out as part of this project on, or in relation to, a person who lacks capacity to consent to taking part in the project.

Relevance of the research to impairing condition

The Committee agreed the research is connected with an impairing condition affecting persons lacking capacity or with the treatment of the condition.

Justification for including adults lacking capacity to meet the research objectives

The Committee agreed the research could not be carried out as effectively if it was confined to participants able to give consent.

Balance between benefit and risk, burden and intrusion

After discussion the REC agreed that the research has the potential to benefit similar patients lacking capacity without imposing a disproportionate burden on this group of participants.

Arrangements for appointing consultees

The REC considered the arrangements set out in the application for appointing consultees under Section 32 of the Mental Capacity Act to advise on whether participants lacking capacity should take part and on what their wishes and feelings would be likely to be if they had capacity.

After discussion, the REC agreed that reasonable arrangements were in place for identifying personal consultees, and that no nominated consultees independent of the project will be sought where no person can be identified to act as a personal consultee.

Information for consultees

The REC reviewed the information to be provided to consultees about the proposed research and their role and responsibilities as a consultee.

The REC was satisfied that the information was adequate to enable consultees to give informed advice about the participation of persons lacking capacity, although some minor changes were required.

Additional safeguards

The REC was satisfied that reasonable arrangements would be in place to comply with the additional safeguards set out in Section 33 of the Mental Capacity Act.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

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Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study:

1. That NIGB approval is obtained to access patient data without consent.

2. As you do not plan to use the SF-36 for those participants who are unable to complete it themselves, then the reference to SF-36 should be removed from the Consultee's PIS.

3. The introductory letter has to come from the patient's clinician introducing very briefly, in a couple of sentences, the study and the researcher. The introductory letter should also have a sentence explaining that the participant's hospital doctor is aware that their patients may be approached about possible participation in the study.

4. The details in both PISs re Post Traumatic Stress should be removed, as it is stress incurred during the interview that is the most pressing concern. The Committee wanted acknowledgement in the PISs that the telephone questions possibly focusing on an individual's current wellbeing and reminding them of their cardiac arrest could be stressful and that the interview could be stopped and the participant given advice to seek help if required from their GP.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which can be made available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

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Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of insurance or indemnity		06 August 2011
GP/Consultant Information Sheets		11 November 2012
Letter from Sponsor		14 November 2012
Letter from Statistician		23 October 2012
Letter of invitation to participant	1.1	28 December 2012
Other: CV Tim Edwards		15 October 2012
Other: CV Julia Williams		01 October 2012
Other: Participant Reply Slip (In Hospital)	1.1	28 December 2012
Participant Consent Form: Patient Consent Form	1.2	28 December 2012
Participant Consent Form: Consultee Declaration Form	1.2	28 December 2012
Participant Information Sheet: Patient Information Sheet	1.2	28 December 2012
Participant Information Sheet: Consultee Information Sheet	1.2	28 December 2012
Protocol	1.2	28 December 2012
Questionnaire: SF-36 telephone version	2	21 January 2013
REC application		14 November 2012
Referees or other scientific critique report		02 November 2012
Response to Request for Further Information		28 December 2012
Summary/Synopsis	Flowchart, v1.2	28 December 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/LO/1911	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp.

Dr Jan Downer
Chair

Email: nrescommittee.london-harrow@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Ms Jill Hollinshead*
Dr Rachael Donohoe, London Ambulance Service NHS Trust
NIGB Ethics & Confidentiality Committee Secretariat

Appendix 6 Health Research Authority Confidentiality Advisory Group approval

NHS
Health Research Authority
Confidentiality Advisory Group

Mr Tim Edwards
London Ambulance Service NHS Trust
Clinical Audit & Research Unit
HQ Annexe
8–20 Pocock Street
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80 London Road
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SE1 6LH

Tel: 020 797 22557
Email: HRA.CAG@nhs.net
http://www.hra.nhs.uk/hra-confidentiality-advisory-group/

10 May 2013

Dear Mr Edwards

Study title: **AMICABLE Airway Management in Cardiac Arrest Study V1.1**
CAG reference: **CAG 1-06 (PR6)/2013)**
IRAS Project ID **101165/414659/4/840**

Thank you for your research application, submitted for approval under the Health Service (Control of Patient Information) Regulations 2002 to process patient identifiable information without consent. Approved applications enable the data controller to provide specified information to the applicant for the purposes of the relevant activity, without being in breach of the common law duty of confidentiality.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether an application should be approved, and if so, any relevant conditions. This application was considered via proportionate review under criteria 1; *Applications to identify a cohort of patients and subsequently to seek their consent.*

Health Research Authority approval decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

- The application is conditionally approved, subject to the standard and specific conditions outlined below.

This letter should be read in conjunction with the outcome letter dated 4 April 2013.

Purpose of application

This application from London Ambulance Services NHS Trust, detailed a study to evaluate the influence of airway management strategies on survival and quality of life where successful pre-hospital resuscitation had taken place.

Support was requested to allow a researcher, employed by London Ambulance Services NHS Trust, access to contact details and survival status in order to contact the patient and seek consent and complete quality of life questionnaires.

Request for clarification

Members asked for clarification over the following points before support could be confirmed, the applicants responses to these points are summarised below:

1. Does the researcher have legitimate access to the database and all data accessed at London Ambulance Services NHS Trust as part of their role within the Trust?

It was confirmed that access was required to 2 databases within the Trust. One was the cardiac arrest database which the researcher would not usually have legitimate access to. This database would be accessed in order to obtain contact details for patients in order to seek consent. The London Ambulance Service Patient Report Form would also be accessed prior to consent, however the researcher had legitimate access to this data without consent as part of their role within the London Ambulance NHS Trust.

2. Please could you confirm what clinical information will be accessed at the London Ambulance Services NHS Trust, prior to ascertaining survival status and seeking consent?

It was confirmed that only demographic information sufficient to ascertain survival status in conjunction with the relevant Heart Attack Centre and enable the care team to make contact with the potential participant would be accessed. This would include patient name, date of birth, address and NHS number. In addition, the London Ambulance Service Patient Report Form would be access which included clinical interventions and associated timings.

3. If a patient was found to be deceased, members requested clarification in relation to what information would then be required in order to include the patient in the study?

The applicant confirmed that information contained within the Patient Report Form and from the Heart Attack Centre would be used within the study. In response to queries from members, the applicant confirmed that where patients are deceased contact will not be made with a legal representative, but access will take place with support under the Regulations.

4. How will data from those who have not provided consent or cannot be contacted be managed? How long will data be retained for these individuals in an identifiable format?

It was confirmed that where an individual could not be contacted or did not provide consent, their data would not be included within the study. Participants would be approached for consent within 30-40 days of treatment.

5. Please could you confirm the process of anonymising the data, in particular given members advice that a dataset containing NHS numbers would be considered identifiable?

Access to identifiable data would be required in order to facilitate the consent process. Once the consent process had taken place all identifiable data would be removed and a unique reference number would be created.

Confidentiality Advisory Group advice

Members reviewed the additional information provided and agreed that the responses were satisfactory and that the minimum criteria under the Regulations appeared to have been met, and therefore advised recommending conditional support to the Health Research Authority, subject to compliance with the specific and standard conditions of support as set out below:

Specific conditions of support

1. Confirmation of final favourable opinion from REC. **Received.**

2. Confirmation of satisfactory security review. **Confirmed.**

3. The amendment of the patient information materials to include clear reference to informing patients how they can opt out of their data being used in the study.

4. The initial approach should include a cover letter from the clinical care team and if telephone contact is to be made prior to consent, this should be by a member of the patients clinical care team.

As the above conditions have been accepted or met this letter provides confirmation of final approval. I will arrange for the register of approved applications on the HRA website to be updated to reflect this information.

Annual review

Please note that this approval is subject to submission of an annual review report to show how you have met the conditions or report plans, and action towards meeting them. It is also your responsibility to submit this report 6 weeks prior to the anniversary of your final approval and to report any changes such as to the purpose or design of the proposed activity, or to security and confidentiality arrangements.

Approved documents

The documents reviewed were:

Document	*Version*	*Date*
REC favourable opinion letter	v 2	04/02/2013
Research protocol	v 1.2	28/012/2013
IRAS application form	v 3.4	15/03/2013
Patient consent form	v 1.2	6/03/2013
Patient information leaflet	v 1.3	6/03/2013
Query sheet response		11/03/2013
Response to clarifications		05/04/2013

Membership of the Committee

The members of the Confidentiality Advisory Group who considered this application are listed below.

Please do not hesitate to contact me if you wish to discuss this letter, I would be grateful if you could quote the above reference number in all future correspondence.

Yours sincerely

Claire Edgeworth
Deputy Confidentiality Advice Manager

Email: CAG.HRA@nhs.net

Copy to: nrescommittee.london-harrow@nhs.net

Confidentiality Advisory Group
Members who considered the application

Group members

Name	Capacity (Lay, expert)
Dr Mark Taylor (Chair)	Lay
Dr Robert Carr	Expert
Dr Christopher Wiltsher	Lay

Appendix 7 Binomial logistic regression model incorporating final airway approach, witnessed arrest, bystander CPR and shockable rhythm

	Block 1		Block 2		Block 3		Block 4	
Variable	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald
Final Airway	.681 (.335-1.383)	1.130 (1df, p=.288)	.683 (.335-1.390)	1.108 (1df, p=.293)	.668 (.326-1.369)	1.216 (1df, p=.270)	.725 (.337-1.561)	.676 (1df, p=.441)
Witnessed Arrest			1.039 (.466-2.317)	.009 (1df, p=.926)	.990 (.440-2.226)	.001 (1df, p=.980)	.552 (.216-1.414)	1.534 (1df, p=.216)
Bystander CPR					1.809 (.950-3.447)	3.250 (1df, p=.071)	1.323 (.660-2.650)	.623 (1df, p=.430)
Shockable							9.798 (3.534-27.164)	19.244 (1df, p=<.001)
Model Chi Square (df)	1.170 (1df, p=0.279)		1.178 (2df, p=.555)		4.545 (3df, p=.208)		33.152 (4df, p=<.001)	
Block Chi Square (df)	1.170 (1df, p=0.279)		.009 (1df, p=.926)		3.367 (1df, p=.067)		28.607 (1df, p=<.001)	
% correct predictions	71.8		71.8		71.8		71.8	
Naglekerke R Square	0.008		0.008		.031		.221	

Appendix 8 Binomial logistic regression model incorporating final airway approach, arrival to ROSC interval, shockable rhythm, and age

	Block 1		Block 2		Block 3		Block 4	
Variable	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald
Final Airway	.713 (.350-1.453)	.866 (1df, p=.352)	.779 (.361-1.679)	.407 (1df, p=.524)	.872 (.381-1.999)	.104 (1df, p=.747)	.904 (.374-2.189)	.050 (1df, p=.824)
Arrival to ROSC interval			.920 (.889-.953)	21.942 (1df, P<0.001)	.927 (.896-.960)	18.497 (1df, p<.001)	.921 (.887-.955)	19.515 (1df, p<0.001)
Shockable					8.693 (3.182-23.455)	17.903 (1df, p<.001)	6.239 (2.228-17.472)	12.145 (1df, p<0.001)
Age							.941 (.913-.971)	14.366 (1df, p<0.001)
Model Chi Square (df)	.892 (1df, p=.345)		32.990 (2df, p<0.001)		58.343 (3df, p<0.001)		74.795 (4df, p=<0.001)	
Block Chi Square (df)	.892 (1df, p=.345)		32.098 (1df, p<0.001)		25.353 (1df, p<0.001)		16.452 (1df, P<0.001)	
% correct predictions	71.5		73.9		77.8		80.7	
Naglekerke R Square	.006		.211		.352		.435	

Appendix 9 Binomial logistic regression model incorporating arrival to ROSC interval, shockable rhythm, and age

	Block 1		Block 2		Block 3	
Variable	OR (95% CI)	Wald	OR (95% CI)	Wald	OR (95% CI)	Wald
Arrival to ROSC interval	.920 (.889-.953)	22.191 (1df, p<0.001)	.927 (.896-.960)	18.6 (1df, p<0.001)	.920 (.887-.955)	19.592 (1df, P<0.001)
Shockable			8.706 (3.210-23.615)	18.06 (1df, p<0.001)	6.276 (2.242-17.563)	12.236 (1df, p<0.001)
Age					.941 (.913-.971)	14.397 (1df, p<0.001)
Model Chi Square (df)	32.577 (1df, p<0.001)		58.239 (2df, P<0.001)		74.745 (3df, p<0.001)	
Block Chi Square (df)	32.577 (1df, p<0.001)		25.662 (1df, p<0.001)		16.507 (1df, p<0.001)	
% correct predictions	73.9		78.3		81.6	
Naglekerke R Square	.209		.352		.435	