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Out-of-hospital cardiac arrest (OHCA) in Queensland, Australia – Epidemiology and predictors of outcome

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Statement of Contribution

Statement of contribution by student

I, Katherine Pemberton, as a PhD candidate of James Cook University, was primarily responsible for the following:

- Conceptualisation and design of the entire research project
- Coordination of the entire study including data collection and analysis
- Ethics/approval applications and data requests
- Liaison with key stakeholders
- Submission of all reports and updates
- Coordination of supervisors
- Drafting manuscripts and coordinating co-author contributions

Supervision

- Dr Kerrianne Watt was my primary advisor, contributing throughout (2013-2020)
- Dr Richard Franklin, Dr Emma Bosley and Dr Peter Aitken were all secondary advisors and contributed when required and available

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- The provision of data was by The Information Support Research and Evaluation Unit (ISREU), Queensland Ambulance Service (QAS) and The Data Linkage Unit (DLU), Queensland Health

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- JCU cohort group – Provision of flights and accommodation for cohort weeks
- JCU student support account - Assisted with covering additional costs such as the purchase of required software

Statement of contribution by co-authors

The authorship team for all manuscripts consists of the candidate and members of the supervisory team only.

Chapter no.	Details of publication(s) on which each Chapter is based	Nature and extent of input from each author
2	Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**. Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment - Part B: non-pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.	Pemberton, Franklin and Watt developed the research question. Pemberton and Watt constructed the search criteria, Pemberton conducted the search. Watt undertook quality assurance processes on inclusion and exclusion. Pemberton grouped the strategies, consolidated the findings and wrote the first draft of these articles, which were critically reviewed by Watt. All authors contributed to the editing of the final manuscript.
4	Pemberton K, Bosley E, Franklin RC and Watt K. Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia. *Emergency Medicine Australasia*. 2019; **31**: 821-9.	† Pemberton, Bosley and Watt developed the objective and outcomes. Pemberton and Watt developed the statistical methods. Pemberton performed the data analysis with assistance from Watt. Pemberton wrote the first draft of the article which was critically reviewed by Watt. All authors contributed to editing the final manuscript.

5	Pemberton K, Bosley E, Franklin RC and Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002–2014): Trends over time. *Emergency Medicine Australasia*. 2019; **31**: 813-20.	† Pemberton, Bosley and Watt developed the objective and outcomes. Pemberton and Watt developed the statistical methods. Pemberton performed the data analysis with assistance from Watt. Pemberton wrote the first draft of the article which was critically reviewed by Watt. All authors contributed to editing the final manuscript.
6	Pemberton K, Franklin RC, Bosley E and Watt K. Long-term outcomes of out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): incidence and temporal trends. *Heart. In press.* 2020.	† Pemberton and Watt developed the objective. Pemberton and Watt developed the outcomes and statistical methods. Pemberton performed the data analysis with assistance from Watt. Pemberton wrote the first draft of the article which was critically reviewed by Watt. All authors contributed to editing the final manuscript.
7	Pemberton K. and Watt K. Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics. *In preparation.*	† Pemberton and Watt developed the objective and the statistical methods. Pemberton performed the data analysis with assistance from Watt. Pemberton wrote the first draft of the article which was critically reviewed by Watt. All authors contributed to editing the final manuscript.

†All authors contributed to developing the data linkage methodology required upfront for these studies. Pemberton collected the linked data and developed and undertook the merging process and analysis.

List of publications

This thesis contains a number of Chapters which have been published or accepted (and one in preparation). Chapter 1 contains a summary of these publications, and the thesis outline. Below is a list of publications contained within this thesis, and other publications and conference abstracts accepted during the candidature.

Thesis publication details:

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment - Part B: non-pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

Pemberton K, Bosley E, Franklin RC and Watt K. Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia. *Emergency Medicine Australasia*. 2019; **31**: 821-9.

Pemberton K, Bosley E, Franklin RC and Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002–2014): Trends over time. *Emergency Medicine Australasia*. 2019; **31**: 813-20.

Pemberton K, Franklin RC, Bosley E and Watt K. Long-term outcomes of out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): incidence and temporal trends. *Heart. In Press.* 2020.

Pemberton K. and Watt K. Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics. *In Preparation.*

Other publications during candidature:
The candidate was an author on several additional published manuscripts during her candidature. These can be viewed in Appendix A.

Every reasonable effort has been made to gain permission and acknowledge the owners of copyright material. I would be pleased to hear from any copyright owner who has been omitted or incorrectly acknowledged.

This thesis includes four published manuscripts - two published in Australasian Journal of Paramedicine and two published in Emergency Medicine Australasia. Advice provided by the journal's editorial offices regarding copyright requirements has been followed (Appendix B). Of the two remaining manuscripts included in this thesis, one has been accepted for publication in Heart and one will be submitted for publication imminently.

Conference presentations during candidature:
Presentations undertaken by the candidate during her candidature can be viewed in Appendix C.

Abstract

Background:
Cardiac arrest is a global health problem and proves a large burden on public health. The majority of events occur out-of-hospital, so management is a priority for ambulance services and survival measures are key performance indicators.

In recent times exceptionally high rates of long-term survival from out-of-hospital cardiac arrest (OHCA) were observed in small population pockets, which sparked interest to achieve this success more broadly. Consequently, the volume of published research rapidly increased, particularly investigating strategies to improve patient outcomes from OHCA. At the commencement of this thesis, some specific reviews of individual strategies to improve outcomes had been undertaken, but none investigating strategies more generally, or to consolidate the findings, and none focused purely on Emergency Medical Service (EMS) provided care in the pre-hospital environment.

The rising interest also led to an increase in reporting. However, there are important gaps in the literature, as follows. Firstly, outcomes are usually reported as proportions of the OHCA population, even though population-based incidence of outcomes provides a more meaningful public health measure. Secondly, while there are published studies of temporal trends in OHCA incidence, there are none reporting temporal trends in OHCA incidence by outcome, and the outcomes from OHCA reported are usually short term, such as survival to hospital. Reporting long-term outcomes, such as survival to 365 days or beyond, better informs strategy development and service provision. Thirdly, while it is well known that the prevalence and prognosis of medical conditions, particularly those of a time critical nature such as OHCA, are impacted negatively by increasing geographical remoteness and disadvantaged socio-economic status, there have been no published studies investigating incidence of short and long-term outcomes by remoteness and/or socio-economic status. The aim of this thesis is to address these gaps.

Objectives:

The aims of this research are: 1) To explore current literature in relation to resuscitation strategies in a pre-hospital setting to improve outcomes from OHCA; 2) To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia; 3) To investigate predictors of survival from OHCA.

Methods:

Aim 1 of this research was addressed by conducting a systematic search and review of recent literature to identify strategies that may be used by paramedics to improve outcomes from OHCA.

Aims 2 and 3 were addressed by linking three large independent data sources: 1) Queensland Ambulance Service (QAS) OHCA Registry; 2) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and 3) Queensland Registrar General (RG) Death Registry. The QAS OHCA Registry was used to identify cases. Inclusion criteria were all adult (18+ years) residents of Queensland, who experienced a confirmed cardiac arrest of presumed cardiac aetiology and were attended by QAS paramedics during a 13-year period (2002–2014). The Data Linkage Unit (DLU), Queensland Health, used specialised linkage software which applies deterministic and probabilistic methodologies to link the records, as well as manual clerical reviews where required. All the included QAS OHCA Registry cases and the records from QHAPDC and RG Death Registry with a positively identified link, were provided to the primary researcher for merging and cleaning.

Aim 2 was further addressed by calculating incidence rates overall and for each calendar year by gender, age, remoteness and socio-economic status. Trends in incidence over time were also analysed. Aim 3 was further addressed by using multinomial logistic regression to calculate odds ratios and 95% confidence intervals. Analyses addressing aims 2 and 3 were undertaken by mutually exclusive pre-hospital and long-term outcomes. Outcomes were defined to distinguish resuscitation attempts, any return of spontaneous circulation (ROSC), ROSC sustained to hospital, survival to admission, survival to 30 days and survival to 365 days or more.

Results:

Aim1 - 28 separate studies were identified for inclusion in the final review, incorporating six strategies. These were: use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation; vasopressin administration; thrombolysis administration; and application of therapeutic hypothermia. Overall, the systematic search and review demonstrated that there is a shortage of high-quality evidence for strategies which may be used by paramedics to improve outcomes from OHCA. Further research with more rigorous designs is required for pharmaceutical and non-pharmaceutical strategies, coupled with continued monitoring of the evidence base.

Aim 2 - Over the 13-years of the study period (2002-2014) there were 30,560 OHCA cases for analysis. The annual crude incidence rate of total OHCA events was 73.95 (95%CI: 73.12-74.78) per 100,000 per annum. Rates were typically twice as high in males as they were in females for total events (males: 98.14 (95%CI: 96.78-99.49); females: 50.32 (95%CI: 49.36-51.28)) and each outcome. Similar patterns were observed in age-specific rates, and incidence rates incrementally increased with age. Incidence of total OHCA generally increased as remoteness increased (major cities: 72.39 per 100,000 (95%CI: 71.35-73.45); very remote: 87.01 per 100,000 (95%CI: 59.67-63.46)). There was an inverse association between total OHCA events and socio-economic status (lowest advantage: 81.34 per 100,000 (95%CI: 79.28-83.40); highest advantage: 61.57 per 100,000 (95%CI: 59.67-63.46)).

Incidence of total OHCA events increased significantly between 2002-2014 overall (64.75-76.10 per 100,000; $p<0.001$) and independently in both males (85.79-99.71; $p<0.001$) and females (44.25-53.09; $p<0.001$). Crude incidence of OHCA resulting in no resuscitation and ROSC sustained to hospital increased significantly from 2002-2014 (27.66-40.17 and 6.31-9.99 per 100,000 respectively; $p<0.001$) while events resulting in no ROSC decreased significantly (28.76-24.02; $p<0.001$). Rates of events resulting in ROSC not sustained to hospital did not change over time. Incidence of total admitted events (9.72-10.13; $p<0.01$), events resulting in survival to 30-364 days (0.18-0.42; $p<0.05$) and survival to 365 days and beyond (1.94-4.02; $p<0.001$) increased significantly over time, but no trends were observed for events resulting in survival <30 days.

Similar trends were observed in most age-specific rates and when analyses were adjusted for age and gender; remoteness and gender; and socio-economic status and gender. These trends were reflected in major cities, inner and outer regional areas. There was a significant increase in events resulting in ROSC sustained to hospital in remote areas and no significant trends in very remote areas. Incidence of total OHCA events increased in areas categorised as lower relative advantage, but no trends were observed in areas of higher advantage. Rates of events resulting in ROSC sustained to hospital increased over time in all socio-economic groups. An increase in survival to 365 days and beyond over time was observed in all remoteness categories and most socio-economic status categories.

Aim 3 - Variables positively (and significantly) associated with survival to 365 days after adjusting for all relevant confounders are: an initial shockable rhythm; bystander witnessed events with bystander CPR; paramedic witnessed events; intubation; time of day (midday-2.59pm); and attendance at scene by a Critical Care Paramedic. However, there are some confounders that could not be controlled in the analyses, so results need to be interpreted with caution.

Conclusion:

There is a shortage of high-quality evidence for strategies to improve outcomes from OHCA. Implementation of a modified resuscitation protocol is the only strategy that showed adequate evidence to warrant immediate implementation where feasible.

This in-depth epidemiological analyses of a large, population-based linked dataset of 13-years of pre-hospitally attended OHCA events provides data on incidence and temporal trends of outcome by age and gender, as well as novel and compelling evidence regarding remoteness and socioeconomic status, which have to date been underexplored, and for which there is a known health care gap. This thesis provides essential information for QAS and other developed ambulance services to evaluate implemented strategies and inform future policy and strategy development, alongside service provision. This work provides an important addition to the pre-hospital evidence base and contributes towards excellence in patient care at a population level.

Table of Contents

List of Tables

Note: All tables are consecutively numbered within each Chapter

List of Figures

Note: All figures are consecutively numbered within each Chapter

Acronyms and Abbreviations

Acronym	Definition
ABS	Australian Bureau of Statistics
ACLS	Advanced cardiac life support
ACP	Advanced Care Paramedic
ARC	Australian Resuscitation Council
ARIA	Accessibility/Remoteness Index of Australia
BLS	Basic life support
CCF	Chest compression fraction
CCP	Critical Care Paramedic
CPR	Cardio-pulmonary resuscitation
DCARF	Death and cardiac arrest report form
DOB	Date of birth
DLU	Data Linkage Unit
eARF	electronic Ambulance Report Form
ECMO	Extra-corporeal membrane oxygenation
ED	Emergency Department
EMS	Emergency Medical Service
ERP	Estimated residential population
HHS	Hospital and Health Care Services
ICU	Intensive Care Unit
ILCOR	International Liaison Committee on Resuscitation
IO	Intra-osseous
ISREU	Information Support, Research and Evaluation Unit
IV	Intra-venous
LAC	Local Ambulance Committee
LASN	Local Ambulance Service Network
LMA	Laryngeal mask airway
OHCA	Out-of-hospital cardiac arrest
OIC	Officer in charge
PEA	Pulseless electrical activity
PCI	Percutaneous coronary intervention
QAS	Queensland Ambulance Service

QAS OHCA Registry	Queensland Ambulance Service Out-of-Hospital Cardiac Arrest Registry
QHAPDC	Queensland Hospitals Admitted Patient Data Collection
RCT	Randomised controlled trial
RG Death Registry	Registrar General Death Registry
ROSC	Return of spontaneous circulation
SA2	Statistical Local Area – level 2
SEIFA	Socio-Economic Indexes for Areas
SES	Socio-economic status

A glossary of commonly used terms can be found in Appendix D.

Preface

Personal background and motivation

My career in pre-hospital care started in 1999 when I commenced a BSc with Hons in Paramedic Science, at the University of Hertfordshire, UK. This was conducted in collaboration with The London Ambulance Service (LAS) and was only the second year a degree level paramedic program had been offered in the UK. Before then ambulance and paramedic training had been via a direct entry process within an ambulance service.

On qualification and graduation in 2002, I naturally transitioned into working for the LAS as a paramedic. I did a variety of clinical roles in London including working on frontline ambulances, single response cars, the cycle response unit and as a Paramedic Team Leader. In 2010 I moved to Australia and began working for The Queensland Ambulance Service, initially as an Advanced Care Paramedic and then as a Critical Care Paramedic (CCP) from 2011 onwards. My experience as a CCP has been broad including pod work, CCP student supervision, flight CCP and various positions in local and state education. I have also worked in The QAS Medical Director's Office on projects involving cardiac care and policy development and alongside several years of this PhD I was A/Manager Cardiac Outcomes in The QAS Information Support Research and Evaluation Unit.

I have always been interested in my own education and development as a paramedic so alongside my work commitments, I have undertaken other roles such as ALS instructor for the UK and Australian Resuscitation Councils and tutoring in pre-hospital and research subjects across several Australian Universities.

During my career, development of the paramedic profession has been vast. This has included continually increasing scope of autonomous practice, specific degree level entry requirements, continued professional development expectations/opportunities and the introduction of paramedic registration requirements (2007 in the UK and 2018 in Australia). I see these as exciting developments in my field and have always had a lust to drive this further.

I came to this research topic through my ongoing interest in advanced life support and a simple but passionate belief that better outcomes could be achieved for more cardiac arrest patients. I began researching ways in which I could contribute to this, which I initially envisaged as conducting a clinical trial/s investigating new methods/equipment for use by paramedics. As I progressed, it became clear that large high-level epidemiological analyses of OHCA cases in Queensland were required to inform any future clinical trials. This along with my interest in epidemiology and biostatistics consolidated the pathway of my PhD.

The undertaking of this PhD has been a mammoth learning curve in many areas and is an experience I will never forget! I have learnt a lot about many areas that would seem obvious, but it has provided me some valuable people management experience and a great insight into myself.

There are very few paramedics with pre-hospital focused PhDs the world over and there are no specific development pathways in ambulance services where PhDs are required. Therefore, although there was a personal development/challenge component to my motivation to undertake this PhD, my main motivation was to be at the forefront of paramedics informing their own practice and further drive the paramedic profession forward.

Paramedic led research is in its infancy in Australia and this thesis makes an important contribution. As the profession continues to develop, opportunities for clinical research to develop will become important measures of credibility in this profession. As far as we know this PhD is one of the first in a clinically focused pre-hospital topic by a practicing Critical Care Paramedic in Queensland. This shows huge development in this field. I am pleased to be amongst the early contributors and hope that this thesis provides a platform against which other paramedics could consider a research contribution to this profession.

I hope the findings and undertaking of this PhD are viewed as positive developments in this field and I hope other paramedics will be encouraged to take on research in pre-hospital areas that are of specific interest to them.

Chapter 1: Introduction

1.1 Overview

This introduction provides background on the OHCA field globally and the context for my research. It positions my work in the evidence base, provides an overview of the thesis, summarises the Chapters and describes the significance of this work.

Table 1: Definitions

A Glossary including a full list of definitions can be found in Appendix D. However, definitions relevant to this Chapter are replicated here.

Cardiac arrest - The condition when a patient is unresponsive and pulseless

Out-of-hospital cardiac arrest (OHCA) – Any case where the patient has been in cardiac arrest while in the presence of QAS responders and the cardiac arrest has primarily been managed by those QAS responders (independent of location)

Resuscitation attempt – Where the total duration of the QAS resuscitation attempt ≥5mins or an ALS procedure has been attempted at any time during the cardiac arrest. If the resuscitation attempt is less than 5 mins and an ALS procedure was not attempted, the case is still classified as a resuscitation

1.2 Background

Cardiovascular disease and sudden cardiac arrest are a major cause of death worldwide. In Australia alone, sudden cardiac arrest kills over 30,000 people per year[1], with the majority of events occurring out-of-hospital[2, 3]. As such, management of OHCA is a priority for ambulance services and survival measures such as ROSC sustained to hospital, are routine key performance indicators.

Incidence and prognosis of OHCA differ globally[4, 5]. In Australia there are approximately 25,000 OHCAs annually[2]. In Queensland, there were 5,301 cases in 2017, of which 2149 (41%) received a resuscitation attempt[6].

While there have been many changes in the management of cardiac arrest in recent decades, it remains a clinical condition characterised by a poor prognosis[7], with overall survival commonly reported at 10-15%. Additionally, survivors often require resource intensive procedures, long stays in ICU and extensive rehabilitation, so this condition proves a large burden on public health.

OHCA and aetiology

Cardiac arrest refers to a state whereby the heart is no longer producing a detectable cardiac output. This is routinely diagnosed by unresponsiveness, absence of normal breathing and lack of a palpable carotid pulse. There are multiple aetiologies of OHCA, the most prevalent is presumed cardiac disease. This represents 65% of the cardiac arrest population in Queensland[8] which is consistent with reports from other developed countries[9, 10]. Cardiac disease may cause a sudden hypoxic insult and subsequent ischaemia to a proportion of the myocardium. This results in a reduced margin between the membrane and threshold potentials of the affected myocytes, increasing their susceptibility to automaticity. This state of hyper-excitation is a precursor to VF, which is the usual initial cardiac arrest rhythm in cardiac arrest from cardiac aetiology. OHCA from cardiac aetiology is the focus of this programme of work.

Management and governance

OHCA requires immediate management, without which the patient will quickly die. There are some aetiology-dependent components of management, but sound implementation of the chain of survival[11, 12] is an essential contributory factor determining success in most cases (Figure 1). This is certainly the case for OHCA of cardiac aetiology.

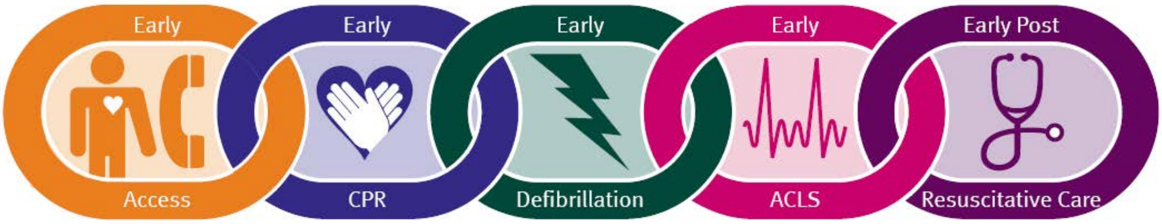

Figure 1: The chain of survival[8]

It is increasingly apparent that successfully addressing the chain of survival requires a systems-based approach[13, 14]. Multiple strategies forming successful systems that transition through every stage will consistently provide the highest level of care and improve outcomes; hence the overlapping of the separate components. A multi-disciplinary approach including pre-hospital services, emergency departments, catheter laboratories, intensive care units, hospital wards and rehabilitation facilities is required.

International resuscitation treatment recommendations are informed by International Liaison Committee on Resuscitation (ILCOR). ILCOR is an interdisciplinary medical advisory group that was conceived in 1992[15] and since 2000 has facilitated 5-yearly reviews of resuscitation science and resultant recommendation updates[16]. Two recommendation updates occurred during the data collection timespan of this PhD (2005 and 2010)[17, 18]. There was a further update in 2015[19] and the next one is expected in 2020. Recent research has shown that high quality BLS is essential to achieve preferred outcomes. High quality BLS requires early defibrillation (where required) and high quality chest compressions; the critical components of which are a rate>100, depth>5cm, minimal interruptions with a chest compression fraction (CCF)>80%, ensuring full chest recoil and avoiding excessive ventilation[20]. This has been reflected in the updated recommendations by ILCOR, which has been replicated in resuscitation council and ambulance service guidelines (Appendix E – Legislation and governance).

OHCA research

In comparison with other disciplines, research on OHCA in the pre-hospital field is developing. Historically, pre-hospital practice has often been determined by in-hospital research and practice. Over time it has been accepted that in-hospital findings are not always transferrable to the pre-hospital field, so the importance of pre-hospital research to inform pre-hospital practice has been recognised. In recent times some small population pockets developed exceptionally high rates of preferred outcomes from OHCA, which sparked interest to achieve this success more broadly. Consequently, there has been an increase in research and literature surrounding OHCA, particularly management practices. It has become a topic of great interest that has been researched and written about with many new ideas and points of view. At the commencement of this programme of work, findings on specific strategies to improve outcomes had been collated and reported as systematic reviews and/or meta-analysis, however no work had been published using a systematic literature search to identify all strategies and then describe and consolidate these findings.

Reporting

The rising interest in this field has also resulted in increased reporting. An increasing number of large national and international ambulance services now produce annual reports on OHCA[9, 10, 21]. The first for Queensland has recently been released[6].

There is also an increasing number of larger registries which amalgamate or collect data from two or more organisations. This enables the formation of larger datasets over broader populations and a more in depth and complete insight into patient exposures and outcomes. These include the North American Resuscitation Outcomes Consortium (ROC) Cardiac Arrest Registry[22]; Cardiac Arrest Registry to Enhance Survival (CARES)[23]; The European Registry of Cardiac Arrests (EuReCa)[24]; The Pan-Asian Resuscitation Outcomes Study (PAROS)[25]; and The Australian Resuscitation Outcomes Consortium (AUS-ROC)[26]. The Queensland Ambulance Service (QAS) contributes data to AUS-ROC.

The reporting of OHCA data can be undertaken in many ways due to the variety of possible definitions for variables of the same title. To ensure accurate comparisons, it is essential that definitions are constant across datasets. The Utstein Template and definitions were designed to address this by providing a uniform pattern and set of definitions for reporting results[27]. The Utstein patient group includes all cases of OHCA where resuscitation was attempted, the arrest was bystander witnessed and the initial rhythm was shockable. This provides a standardised patient group on which to calculate survival. It must be acknowledged that these definitions are still open to a degree of interpretation, although this is unlikely to result in large variances in reported statistics. The Utstein template and definitions continue to form the internationally accepted method by which calculations are determined and largely enable international comparisons.

Outcomes

Historically, outcomes that have been routinely collected and reported by many ambulance services are mostly short-term pre-hospital outcomes which are available up to the point of hospital handover, such as return of spontaneous circulation (ROSC) and ROSC sustained to hospital. However, longer term outcomes, such as survival to admission or beyond, are better predictors of patients' ongoing health care needs, quality of life and burden on public health. Long-term outcomes have not been routinely reported as they require data linkage with hospital and death records, which is resource intensive and time consuming. This has been a limitation of many large pre-hospital datasets for many years and has posed a major barrier to potential studies. There are exceptions to this, such as in Western Australia where ambulance OHCA data has been linked and long-term outcomes reported (internally) since 1996. In some cases, survival data has been provided to the ambulance service in summary format (e.g., proportion of patients that survived to hospital discharge by shockable status), as has been the case in QAS until recently. Although accurate data collection and reporting to any extent is valuable, data linkage for each individual patient is more useful and therefore preferable. Alternatively, ambulance services have been limited to the information collected themselves. In more recent times, with an increased understanding of the importance of reporting long term outcomes, this has been overcome by the establishment of methods to routinely link specific ambulance and hospital data in many services. These methods have been in place in QAS since 2017 and was an extremely positive step moving forward. Nevertheless, trends over time analyses of long-term outcomes is still limited as this process has not been undertaken retrospectively.

Contemporary understanding of OHCA outcomes includes the importance of measuring and reporting on neurological function and health-related quality of life[28], as well as survival measures by time. Neurological and quality of life measures are more informative of the true burden of OHCA, but are not routinely available, so can be difficult and time consuming to collect. Additionally, more traditional outcome measures, such as survival to hospital and/or specified time periods, are not fully understood, so it is imperative investigations in this area continue.

Nevertheless, neurological and quality of life measures are not the focus of this thesis. This thesis explores the epidemiology of multiple pre-hospital and long-term outcomes over four Chapters. The relevant outcome definitions are provided at the beginning of each chapter, alongside a clear description of the preferred and least preferred outcomes relative to that chapter.

In this thesis, all outcomes are reported as mutually exclusive groups. Although atypical for OHCA reporting, this novel approach allows exploration of the characteristics of each group independently. It also enables epidemiological analyses, such as relative risk, which cannot be done without mutually exclusive groups and therefore fills an important gap in the evidence base.

Incidence

Outcomes from OHCA are routinely reported as proportions of the OHCA population. For example, in Queensland in 2017 32% of cases (Utstein patient group) survived to hospital discharge[6]. Population-based incidence provides a more meaningful public health measure and benchmark of current status as it accounts for changes in population demographics, which continuously occur the world over to different extents. It is known that Queensland has an ageing population and increasing age brings an increased risk of OHCA and poorer outcomes[8], hence, using numbers alone may lead to misinterpretation. Incidence also allows analyses of changes in risk and outcome at a population level, which is particularly useful for strategy evaluation.

Few studies have reported incidence of OHCA outcomes. The EuReCa ONE study reported OHCA outcomes in 27 European countries in one month[29]. Population incidence rates (per 100,000 per year) were reported by country for resuscitation attempts (range 19-104), return of spontaneous circulation (ROSC) (range 6-32), survival (range 0.2-17.3) and survival in bystander witnessed events of suspected cardiac aetiology with an initial shockable rhythm (range 0.1-6.3).

Other studies reporting incidence have focused on trends in rates of OHCA over time, but not by outcome[30-37]. Five studies investigated patients who received a resuscitation attempt only, three of which (conducted in Rochester, Minnesota, US; Seattle, US; and Helsinki, Finland) showed declining incidence rates over time in patients with a shockable rhythm[30-32]; one (from Milwaukee, Wisconsin, US) showed declining rates in shockable cases, an increase in rates of asystole and no change in rates of PEA[33]; and one (from the US) reported an increase in overall incidence and in every presenting rhythm[36]. One (Ontario, Canada) study investigated OHCA patients who had not died on ED arrival and found no change over time (2002-2012) in age- and gender-standardised (36 per 100,000 per annum) and gender-specific incidence (female - 24.5, male - 48.1 per 100,000 per annum)[37]. The remaining two were Australian studies, one in Western Australia (1997-2010)[34] and one in Queensland (2002-2014)[35]. As well as trends over time, they both reported mean annual incidence rates per 100,000 of the population: 69.8 and 85.4 (age-standardised), 60.2 and 78.2 (crude) and 355.1 and 322.54 (age-standardised in age 65 years+), respectively. Neither study reported results by outcome.

Trends over time analyses are important to evaluate the impact of population changes and the success of implemented prevention strategies and development of new ones. Further, trends over time analyses of incidence by outcome allow the evaluation and development of future management strategies.

Geographical remoteness and socio-economic status

The prevalence and prognosis of medical conditions, particularly those of a time critical nature such as OHCA, are impacted negatively by increasing geographical remoteness and disadvantaged socio-economic status (SES)[38]. Several studies have explored outcomes from OHCA by remoteness, but not incidence of outcomes[5, 39-43]. Similarly, there are studies that have examined incidence of OHCA events in relation to SES[44, 45] and studies evaluating the impact of various measures of SES on outcome[46-51], but none have reported incidence of outcomes. This is an important gap in the evidence base.

Queensland and QAS

The state of Queensland covers a large area consisting of over 1.8 million km^2. Over half the Queensland border is coastline comprised of multiple towns within which the majority of its approximately 5 million people reside[52]. The south-east corner is by far the most densely populated region. Queensland has a high proportion of its population living outside major cities compared to other states (38% versus 23-27% respectively)[53]. The huge diversity in geography and remoteness of much of this region provides many challenges when providing access to health care services as demonstrated within the Cardiac Accessibility and Remoteness Index for Australia (ARIA) Project[54]. In addition, Queensland has an ageing population which is an identified risk factor for many health conditions including OHCA, providing a further challenge to meeting care requirements.

QAS services are delivered through 15 Local Ambulance Service Networks (LASNs), aligned with the State's Hospital and Health Care Services (HHSs) (Figure 2). There are over 4,100 employees and 296 ambulance response locations[55]. These are mostly permanent ambulance locations but also consist of hospital-based locations, airports, field offices and locations with first responders and/or honorary officers. In addition to road responses, aeromedical and helicopter retrieval services are also available, coordinated under the governance of the Department of Health.

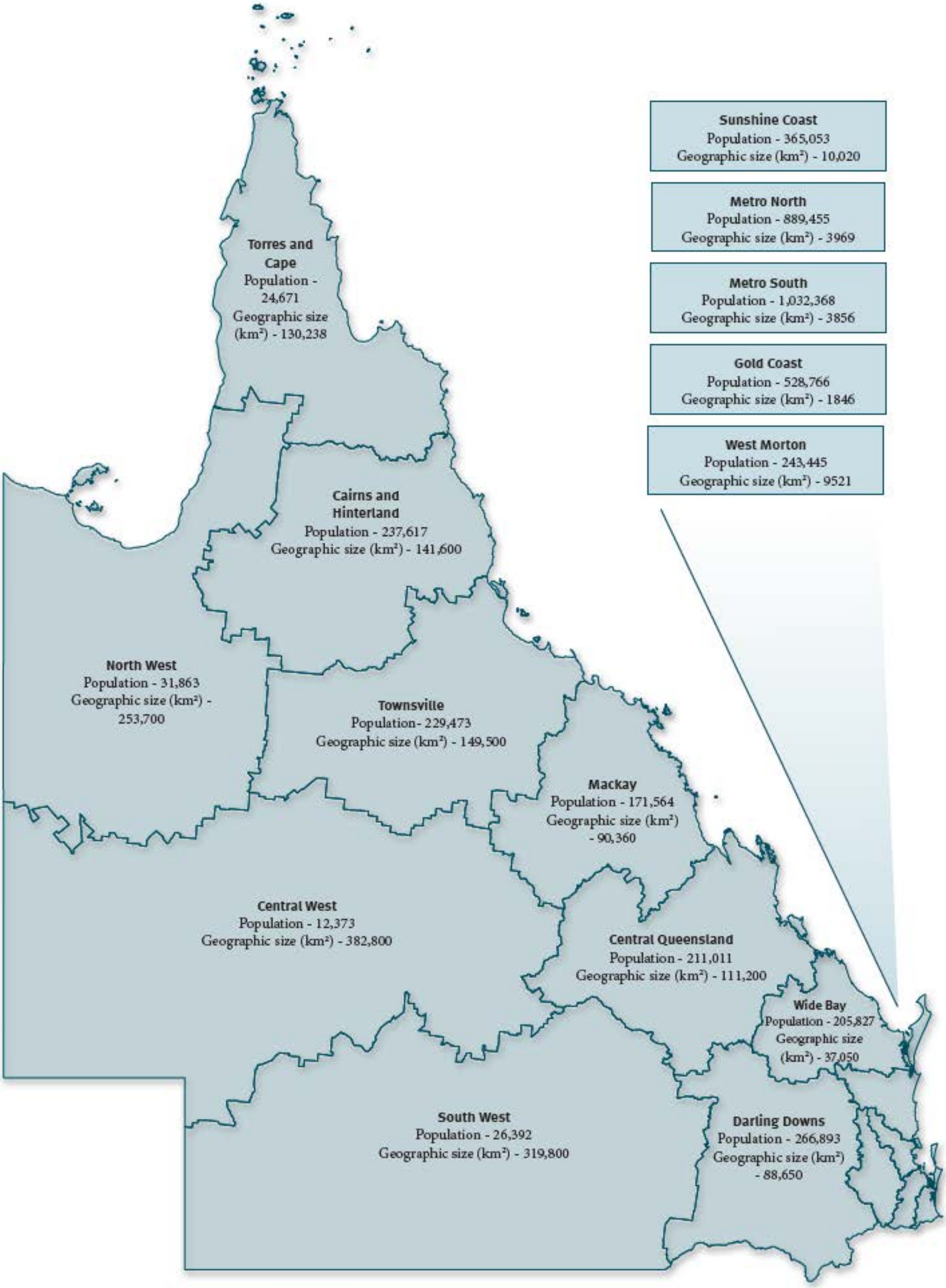

Figure 2: Map of Queensland and Local Ambulance Service Networks[8]

The QAS provides emergency and routine pre-hospital patient care and transport services as well as other community services such as first aid training, to the people of Queensland[55]. A larger part of this responsibility involves responding to over 600,000 emergency cases each year. Activation and response to these cases is immediate and with or without the use of emergency lights/sirens (known as code 1 and 2 response respectively). Of these, 0.5-1% are patients who are either already in cardiac arrest or whose condition subsequently deteriorates to that state before hospital arrival. In Australia, emergency ambulance requests are made through a single national telephone number (000). There are seven operations centres across the state of Queensland triaging the relevant calls.

Where resources allow, OHCA cases routinely receive two Advanced Care Paramedic (ACP) crews (equating to four ACP officers) and a Critical Care Paramedic (CCP) as a single responder. ACPs have BLS and ALS skills including LMA placement and IV fluid/adrenaline administration, while the skills of CCPs extend further to include intubation, IO access and critical care drugs and procedures.

1.3 Aims

The aims of this programme of research were constructed with an intention to inform ways to improve outcomes from OHCA. QAS have a rich dataset on OHCA and require large epidemiological studies to benchmark current status and inform strategy development and service provision. Consequently, the aims of this research are:

1) To explore current literature in relation to resuscitation strategies that could be used by paramedics in a pre-hospital setting to improve outcomes from OHCA
2) To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia
3) To investigate predictors of survival from OHCA

1.4 Thesis Outline

Figure 3 presents the conceptual model of this thesis, designed to guide the reader through the work. This is a thesis by publication. The programme of work consists of four articles published in peer reviewed journals, one article submitted for publication and currently under review and one article in the process of being formatted for submission for publication. This forms Chapter 2 and 4-7 of this thesis. Publications 1-4 are presented in the format in which they have been published (PDF), and articles 5 and 6 are presented in the format required by the journals to which they have been / will be submitted for consideration of publication. There is some inevitable overlap through this thesis. References are self-contained within each Chapter. References are presented at the end of each publication or at the end of the Chapter in Chapters that do not contain a publication. There is deliberately no reference section for the thesis as a whole. Each Chapter starts with an overview of the contents and concludes with a summary of the important points from the Chapter.

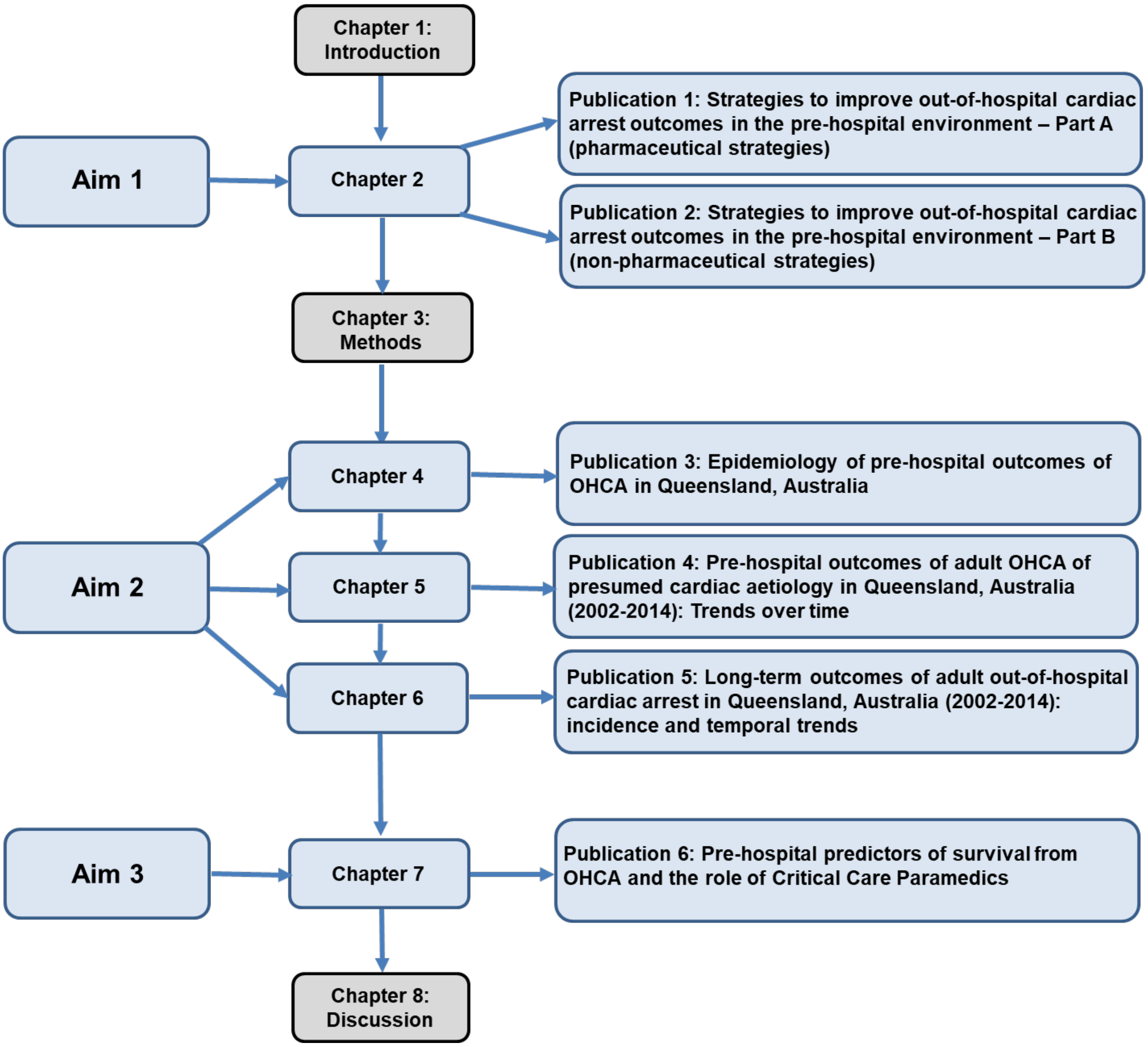

Figure 3: Conceptual model of thesis

Summary of Chapters and corresponding publications

Chapter 1

The thesis starts with the Introduction (Chapter 1, current Chapter). As well as some global background on the OHCA field, the context for my research is described, including the Queensland Ambulance Service. The thesis structure and significance of the work are described.

Chapter 2 [Publications 1&2]:

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment - Part B: non-pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

Chapter 2 addresses aim 1 *(To explore current literature in relation to resuscitation strategies in a pre-hospital setting to improve outcomes from OHCA)* and comprises two published articles. These articles, published in the Australasian Journal of Paramedicine, describe the results of a systematic search and review investigating strategies which may be used by paramedics to improve outcomes from OHCA. The broad nature of this topic determined that a single publication was not feasible, so this study was split into two publications: 1) Part A - pharmaceutical strategies; and 2) Part B - non-pharmaceutical strategies. This review identifies strategies, describes and synthesises the evidence and makes recommendations for future strategy development and implementation. This review supported the requirement for large epidemiological studies to inform target populations.

Chapter 3

Chapter 3 presents the methods used for articles 3-6 (Chapters 4-7). The detailed methods for each Chapter are described in the relevant Chapter, but Chapter 3 is a summary of the overall methods for the thesis, providing additional context not possible in the published papers due to publishing constraints, avoiding repetition as much as possible.

Chapter 4 [Publication 3]:

Pemberton K, Bosley E, Franklin RC and Watt K. Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia. *Emergency Medicine Australasia*. 2019; **31**: 821-9.

The article that forms the basis of this Chapter is published in Emergency Medicine Australasia, and addresses aim 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia)* of the thesis. It is the first of two papers reporting the results of a large epidemiological analyses of OHCA in Queensland_(2002-2014) using rigorous data linkage methodology. It reports population-based annual incidence of four mutually exclusive pre-hospital outcomes of adult OHCA of cardiac aetiology in Queensland, Australia by age, gender, geographical remoteness and SES. The sample for Chapters 4 and 5 includes all cases of adult OHCA of presumed cardiac aetiology in residents of Queensland, attended by QAS paramedics in Queensland. The findings from this study provide an important benchmark of the current status and will inform future strategy development.

Chapter 5 [Publication 4]:

Pemberton K, Bosley E, Franklin RC and Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002–2014): Trends over time. *Emergency Medicine Australasia*. 2019; **31**: 813-20.

This Chapter is the second of two articles based on the large epidemiological analyses, and also addresses aim 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia)* of the thesis. This article, published in Emergency Medicine Australasia, reports trends over time in the incidence of pre-hospital outcomes of adult OHCA of cardiac aetiology in Queensland, Australia. Analyses are undertaken by age, gender, geographical remoteness and SES. The findings from this study provide important insight into the success of implemented strategies and further inform future strategy development.

Chapter 6 [Publication 5]:

Pemberton K, Franklin RC, Bosley E and Watt K. Long-term outcomes of out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): incidence and temporal trends. *Heart. In Press.* 2020.

One article accepted for publication in Heart, forms the basis of this Chapter, which is the last Chapter to address aim 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia).* The sample for this Chapter includes all cases of adult OHCA of presumed cardiac aetiology in residents of Queensland, attended by QAS paramedics in Queensland, who survived to hospital admission. The Chapter explores population-based incidence and temporal trends of three mutually exclusive long-term outcomes of adult OHCA (survival to <30 days; survival 30-364 days; survival to 365 days+) of presumed cardiac aetiology in Queensland. Age, gender, remoteness and SES are all investigated. Long term outcomes are more informative measures on the true burden of OHCA than pre-hospital outcomes, so these findings provide a more meaningful benchmark of current status and profound insight for strategy evaluation and development.

Chapter 7 [Publication 6]:

Pemberton K and Watt K. Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics. *In preparation*.

This Chapter addresses the final aim of the thesis *(To investigate predictors of survival from OHCA)* and comprises one article that will be submitted to a peer reviewed international journal. The sample for this Chapter comprises all cases of adult OHCA of presumed cardiac aetiology in residents of Queensland, who received a resuscitation attempt by QAS paramedics in Queensland. This article investigates independent predictors of four mutually exclusive short and long-term outcomes from adult OHCA of cardiac aetiology. The findings inform pre-hospital health care policy development and service provision in Queensland and are transferrable to any other areas with well-developed health care services.

Chapter 8 (Discussion)

The thesis concludes with the Discussion and Conclusion, where the findings from all studies are consolidated in the context of the strengths and limitations of this programme of research and the existing evidence, with a focus on the implications for policy, practice and future research.

Appendices

Appendices follow the thesis Implications and Conclusion. Appendices consist of: Other related publications during candidacy; evidence of the fulfilment of copyright requirements; presentations during candidacy; glossary; legislation and governance; search strategy; ethics and approvals; data sources and variables; and data management.

1.5 Significance of this study

This is the first study in Australasia where population-based incidence rates are reported by outcome. Outcomes are usually reported by proportion of the OHCA population, however incidence accounts for changes in population demographics so is more informative to benchmark current status. The limited international studies reporting incidence by outcome have smaller samples, shorter data collection phases and use fewer/shorter-term outcomes, so this study fills an important gap in the international evidence base. This is also the first study to report temporal trends in OHCA incidence by outcome. The outcomes investigated include mutually exclusive pre-hospital and long-term outcomes (up to 365 days+ survival). Historically, routine data linkage between pre-hospital and hospital/death registry data largely did not occur, so long-term outcomes on an individual patient level were not easily accessible. This study has enabled that linkage and collection over a time period which would otherwise not be evaluated in this way. Additionally, the mutually exclusive nature of the outcome groups is a novel approach, allowing exploration of each group independently and epidemiological analyses such as relative risk, which could not be done otherwise.

This programme of research investigates incidence of OHCA outcomes by remoteness and SES which have not been investigated in this way previously. There is current acute interest in measuring the size of the health gap between remoteness and SES groups[38]. This study will contribute to better inform these gaps and therefore identify ways to reduce them.

Additionally, this is the first time pre-hospital identified patients have been accessed with a primary purpose to provide pre-hospital relevant predictive factors of long-term outcomes of non-traumatic OHCA, and the first time multivariate analyses have been completed to predict outcomes from OHCA in Australasia. This is also the first study to consolidate published findings and make recommendations on strategies to improve outcomes from OHCA broadly and with a focus on EMS delivered care. Understanding outcomes from OHCA is important to ambulance services in developing future strategies[6, 35]. This study provides the basis to evaluate implemented OHCA strategies and will inform future pre-hospital policy development and service provision in Queensland and potentially other areas with developed health care services.

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Chapter 2: Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment

2.1 Overview

This Chapter comprises two publications that collectively address aim 1 of the thesis (to explore current literature in relation to resuscitation strategies in a pre-hospital setting to improve outcomes from OHCA). These two papers were published as a series in the Australasian Journal of Paramedicine, and describe the results of a systematic search and review. This is not a systematic review. This review explores novel strategies (that is, strategies not already currently in use in Australia) that potentially could be used by paramedics in the pre-hospital environment to improve outcomes from adult OHCA of cardiac aetiology in high-income countries with developed health care services.

In recent times, there has been a marked increase in the volume of published research investigating ways to improve outcomes from OHCA. At the time of this literature review, some specific reviews of individual strategies to improve outcomes from OHCA had been undertaken, but none investigating strategies more generally. The intention of this systematic search and review was to provide a broader perspective than previous reviews by systematically searching the literature to firstly, identify strategies to improve outcomes from OHCA and secondly, consolidate the findings. Additionally, this review focuses on EMS provided care in the pre-hospital environment, so is a novel and important addition to the literature.

The broad nature and therefore size of this systematic search and review, determined that publication as an individual body of work was not feasible. Consequently, this review was split into two, Part A: pharmaceutical strategies and Part B: non-pharmaceutical strategies. This split was informed by the groups of strategies identified for review. The search strategy used is outlined in Appendix F.

This Chapter presents both parts (Part A and Part B) of the review. Part A reports the methods used, assembles the identified strategies and reports on the findings of the pharmaceutical strategies only. Part B reports the findings of the non-pharmaceutical strategies only. Figure A shows the position of this Chapter in the thesis.

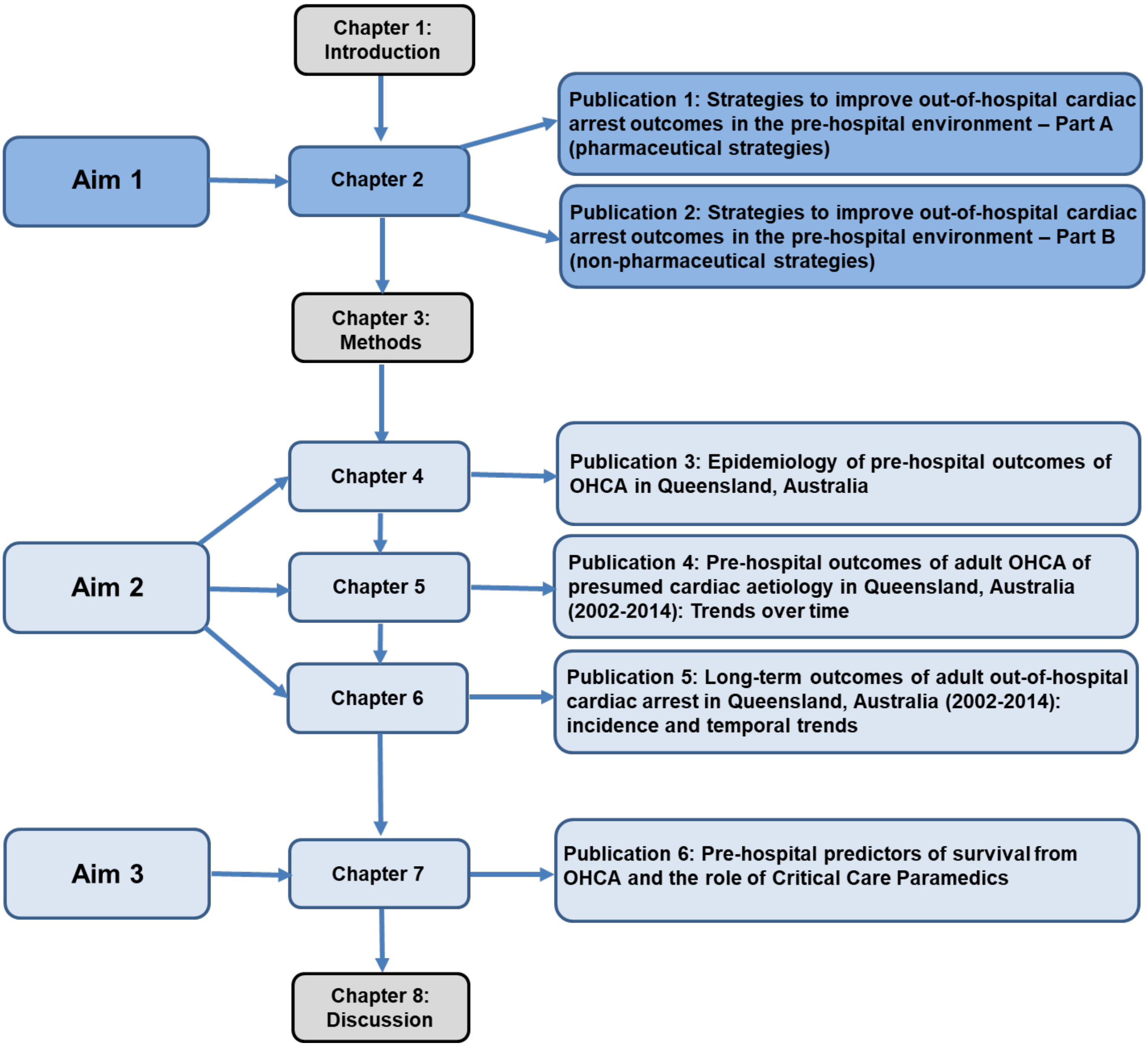

Figure A: Conceptual model of thesis – Aim 1, Chapter 2, Publications 1&2

2.2 Manuscripts

The articles are presented as published:

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

Pemberton KE, Franklin R and Watt K. Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment - Part B: non-pharmaceutical strategies. *Australasian Journal of Paramedicine*. 2019; **16**.

These articles are inserted as published PDFs. Supplementary material supporting these articles is presented immediately after the relevant article, prior to the Chapter summary.

AUSTRALASIAN JOURNAL OF PARAMEDICINE

PARAMEDICS AUSTRALASIA

Review

Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part A: pharmaceutical strategies

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Abstract

Introduction
Historically, survival rates from out-of-hospital cardiac arrest (OHCA) have been low. In recent times, survival rates have increased substantially in some small population pockets, which sparked general interest in this field and the volume of research increased. Included was an increase in the number of strategies being investigated to improve outcomes. The aim of this review is to assemble these strategies and consolidate the findings of the pharmaceutical strategies.

Methods
This is a systematic search and review, rather than a systematic review. Four databases (MEDLINE, CINAHL, Informit, Scopus) were searched for papers published between 2007 and 2017 containing strategies that may be used by paramedics when resuscitating adult (18+ years) patients in cardiac arrest from presumed cardiac aetiology in the out-of-hospital environment. The search was undertaken in February 2017. Five separate search concepts were used on all databases. Each concept consisted of multiple search terms.

Results
This review identified 28 separate studies for final review, which formulated six strategies. These were: use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation; vasopressin administration; thrombolysis administration; application of therapeutic hypothermia. This paper reports on the full results of the pharmaceutical strategies (vasopressin or thrombolysis administration). Part B will address the non-pharmaceutical strategies.

Conclusion
There is no evidence to support the introduction of vasopressin or thrombolysis use during OHCA. Future studies should focus on study design and specific patient subsets.

Keywords:
heart arrest; emergency medical service; advanced life support

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a global health problem with a substantial public health burden. There is disparity in rates of outcomes globally (1). Success from resuscitation is dependent on multiple factors such as aetiology, presenting rhythm, time interval with no treatment, and the quality of treatment provided. Optimal management requires a systematic approach, with every stage of the chain of survival appropriately addressed (2). This includes early identification of OHCA and predisposing symptoms; early activation of emergency medical services (EMS); early high-quality cardiopulmonary resuscitation (CPR); early defibrillation; high quality intra-arrest life support (basic and advanced life support provided by EMS); access and appropriate referral to cutting edge post-resuscitation care services. It is paramount that each component of the system functions flawlessly to ensure the best possible outcomes.

Historically, rates of survival from OHCA have been fairly low, but in recent times high rates of preferred outcomes have developed in small population pockets, which has sparked interest to achieve this success more broadly. This pre-empted an increase in volume of research in the OHCA field and an increase in the number of strategies investigated to improve outcomes. It is timely that a review be undertaken to assemble these strategies and consolidate findings.

The focus of this review is the component of EMS-provided care, which includes intra-arrest and immediate post-arrest life support. This is a systematic search and review (3), rather than a systematic review. Systematic methods were used to search literature, extract data and appraise selected articles. The aim of this review is three-fold: to identify recently investigated strategies aimed at improving outcomes from adult OHCA that could be an addition to current paramedic practice in Australia; to describe the evidence for each strategy; and to synthesise the evidence and make recommendations for improved outcomes from OHCA in high-income countries with developed pre-hospital health care systems. The full search strategy and methods of the study are described in this paper, but the focus of the results is on pharmaceutical strategies. Part B will address the non-pharmaceutical strategies.

Methods

A systematic literature search of four databases (MEDLINE, CINAHL, Informit, Scopus) identified papers published between 2007 and 2017 containing strategies that may be used by paramedics to improve outcomes when resuscitating adult (18+ years) patients in cardiac arrest from presumed cardiac aetiology in the out-of-hospital environment. The search was undertaken in February 2017 and was limited to 2007 onward for pragmatic reasons and to ensure currency (as the paramedic field is rapidly evolving).

Five separate search concepts were used on all databases. Each concept consisted of multiple search terms. The concepts were linked by ‘and’ and the search terms were linked by ‘or’. Search terms consisted of keywords in all databases with the addition of MeSH terms in MEDLINE and major headings in CINAHL (Table 1).

Table 1. Search concepts and respective keyword examples

Search concepts	Keyword examples
1. Incident	Cardiac arrest, heart arrest, ventricular fibrillation, asystole, PEA
2. Environment	Emergency medical service, EMS, ambulance, prehospital
3. Resuscitation attempt	Advanced life support, basic life support, chest compressions, CPR
4. Strategy	Treatment, therapeutic, strategy, initiative, device, equipment
5. Measurable outcome	Survival, prognosis, ROSC, outcome, result, return of output

All papers identified were copied into Endnote (version 7) and duplicates removed. The remaining papers were reviewed by title and abstract for relevance against the inclusion and exclusion criteria (Table 2), and remaining papers were reviewed by full text.

Systematic reviews and meta-analyses were excluded as per ‘primary studies only’ inclusion criteria. However, the studies included in these systematic reviews and meta-analyses were assessed against the inclusion/exclusion criteria for relevance to this literature review. The primary author (KP) conducted the search. The secondary author (KW) reviewed all studies included by title/abstract and one in 10 studies excluded by title/abstract. The few contradictions on inclusion were overcome by discussion between reviewers and consensus was reached. Reference lists of all the included papers were also scanned for further relevant papers.

The findings are presented in two separate papers. This paper (Part A) describes the search methods and results in full, but the results focus on pharmaceutical strategies. Results for the non-pharmaceutical strategies will be presented in Part B. This division of strategies (pharmaceutical and non-pharmaceutical) is due to the current emphasis on high quality CPR and less on drug administration (4) to improve outcomes from OHCA.

Results

This literature search identified 28 separate studies for final review. Figure 1 outlines the results yielded by the described search process.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Strategy identified • Study has a pre-hospital focus • Strategy implemented by health care professional/s on scene • The strategy is plausible (ie. there is scientific suggestion it may provide improvement over current management/ outcomes in OHCA) • OHCA from presumed cardiac or non-specific/all aetiologies • Strategy implemented in the intra-arrest/immediate post-arrest phase • Patient cohort largely 18+ years • Patients identified/allocated to groups (randomly or non-randomly) based on the pre-hospital phase • Evaluation process with control group • Patient outcome measurement as an explicitly stated goal/ present result • Strategy (or larger part thereof) must be an addition to current practice in Australia which aims to inform the progression of current practice • Primary studies only	• Strategy undertaken in the in-hospital environment (or not clear) • Strategy involves transport destination choice only • Strategy implemented before health care professional arrival on scene (ie. community strategies) • Strategy not aimed at improving management/outcomes in OHCA patients • OHCA from non-cardiac aetiology specifically • Patient cohort largely less than 18 years • Strategy (or larger part thereof) is underway or has previously been underway (evidence not subsequent and contradictory to that change) in Australia • Secondary studies (duplicate sample) unless added to another relevant sample or reporting additional relevant endpoints • Pilot studies where the sample has been used as part of a larger sample in another study (duplicate sample) – unless additional endpoints were reported • Stated or inferred safety/feasibility study, in aims, introduction or methods. An example of inference is that the study is intentionally not powered to detect differences in patient outcomes • Published as an abstract only

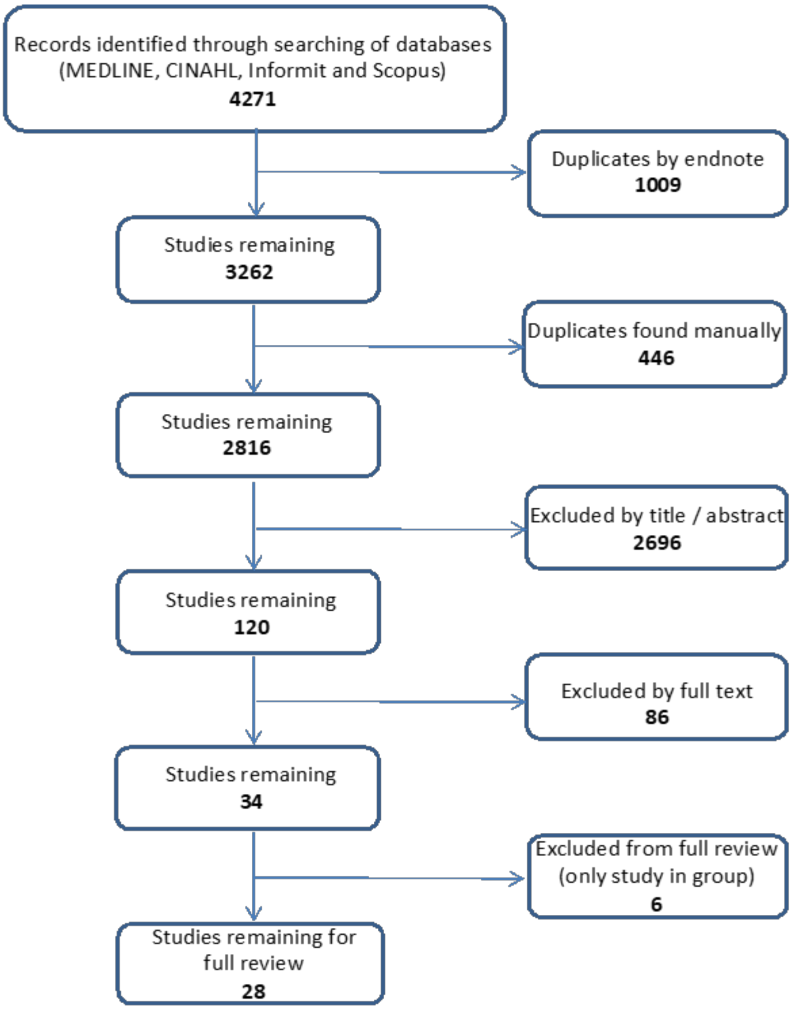

Figure 1. Literature search PRISMA flow diagram

After the process of exclusion by full text, 34 papers remained and were grouped by strategy. There were 12 groups of strategies, however for six of these there was only one relevant paper. These strategies were: passive oxygen insufflation, hypertonic saline administration, erythropoietin administration, lignocaine administration prophylactically, procainamide administration, waveform analysis-guided shock timing. In order to make rigorous recommendations for a strategy (one of the main aims of this review), evidence from more than one study is required therefore these six papers were excluded from the main focus of this review. Six groups of strategies remained, incorporating 28 separate studies for final review (Table 3). Of these, two groups focussed on pharmaceutical strategies (vasopressin or thrombolysis), compiling five studies that are fully presented in this paper (Part A). The remaining non-pharmaceutical strategies will be presented in Part B. Table 4 summarises the characteristics and results of the five studies included in this paper.

Table 3. Strategies and number of papers in full review

Strategy	Number of studies
Use of a modified resuscitation protocol*	7
Use of a mechanical chest compression device	7
Intra-thoracic pressure regulation	3
Vasopressin administration	3
Thrombolysis administration	2
Application of therapeutic hypothermia	6

*This group includes studies in which the modified resuscitation protocol was primarily aimed at improving CPR quality. This strategy was also known as minimally interrupted cardiac resuscitation, cardio-cerebral resuscitation, team-focussed CPR and pit crew approach.

Vasopressin administration

Three papers investigated use of vasopressin in the intra-arrest phase of OHCA (5-7). A double-blind randomised controlled study (RCT) of vasopressin (dose: 40 units with a maximum cumulative dose of 80 units) in conjunction with adrenaline versus adrenaline alone was conducted in France (6). Intention to treat data analysis principles were applied. Overall there were no significant differences between groups for any patient outcome measure (survival to admission, ROSC for ≥1 minutes, survival to discharge, survival with good neurological recovery, survival to 1 year). However, in the subset of pulseless electrical activity (PEA) patients, survival to hospital discharge was significantly more common among controls than cases.

The remaining two studies were both observational and had a data collection period that contained a change in protocol to include vasopressin use (5,7).

The primary endpoints of the prospective study (5) were clinical prognostic factors for outcome (end tidal carbon dioxide [$ETCO_2$] and mean arterial pressure [MAP]), which showed favourable results for vasopressin use. Positive results were also observed in direct patient outcome measures, including significant associations between hospital admission and 24-hour survival with cases in both univariate and multivariate analysis. There were no significant differences between groups in hospital discharge rates, although when the asystole subgroup was examined, hospital discharge rates were significantly higher among cases. Survival to hospital discharge was not reported for other initial rhythm subgroups. However, multivariate analysis in which shockable status was adjusted for, showed that vasopressin administration was not independently associated with hospital discharge, thus it can be assumed there were no significant differences between groups in the shockable subset. Results of the PEA subgroup were not published so remain unknown. Among all patients discharged from hospital in this study, there were significantly more cases with a preferred neurological outcome (CPC 1 or 2).

The case-control study (7) examined survival to ED, survival to 24 hours and survival to discharge, for which no significant differences between groups were found. No further analyses or results were reported.

All three studies (5-7) have some common limitations, including the unavoidable use of a poor prognosis sample (initial rhythm of PEA, asystole or, if shockable, after three unsuccessful shocks), due to the nature of the strategy. Consequently, larger samples than usual were required to provide statistical power to show significance, so the demonstration of cause and effect was harder to achieve and may explain the lack of observed associations. Further limitations of these studies include the absence of quantification of chest compression quality and the lack of standardised in-hospital care, both of which are known to impact on patient outcomes (2,10).

The observational studies (5,7) are both limited by the non-randomised design and the impacts of potential unknown/unmeasured changes in practice over time. The retrospective study allocated cases/controls strictly using the date of protocol change, whereas the prospective study used date of incident and accessibility of vasopressin to allocate patients to groups. Therefore, group allocation was likely to be more accurate (as per question objective) in the prospective study, although the majority of controls were still in the earlier years. In the prospective study, administration of adrenaline alongside vasopressin was not measured, thus it is unknown if the positive results can be attributed to vasopressin alone or a synergistic effect between vasopressin and adrenaline. Due to the nature of the retrospective study, there is greater risk of additional unmeasured and uncontrolled factors contributing to the findings.

Table 4. Evidence table for pharmaceutical strategies to improve OHCA outcomes in the pre-hospital environment

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Vasopressin administration					
2007 Mally (5)	Intra-arrest vasopressin (with/without adrenaline)	Non-randomised trial January 2000 – April 2006	Maribor, Slovenia Data collected from all calls classified as OHCA Intervention group – 146 Non-intervention group – 452	Average $ETCO_2$ in all patients and final $ETCO_2$ (primary outcomes) in patients with ROSC were significantly higher in the intervention group (p<0.01) Average values of initial and final MAP (primary outcomes) were significantly higher in the intervention group (p<0.01) Univariate outcome analysis: The following outcomes were significantly more frequent in the intervention group: ROSC (p=0.04), ROSC and hospital admission (p=0.01) and survival at 24 hours (p=0.02). There were no differences between groups in hospital discharge (p=0.19) Multivariate analysis: ROSC and admission to hospital (secondary outcome) was associated with the intervention group OR 1.63 95% CI: 1.24-2.14. Survival at 24 hours (secondary outcome) was associated with the intervention group OR 1.34 95% CI: 1.14-1.94. Hospital discharge (secondary outcome) showed no association OR 1.12 95% CI: 0.82-1.33	+
2008 Gueugniaud (6)	Intra-arrest vasopressin (in addition to adrenaline)	Double-blind placebo RCT May 2004 - April 2006	France Intervention group – 1442 Non-intervention group – 1452	ITT analysis: No significant differences between groups in survival to admission (primary outcome), ROSC for at least 1 minute, survival to discharge, good neurological recovery (CPC 1), 1 year survival (secondary outcomes)	/
2010 Cody (7)	Intra-arrest vasopressin (in addition to adrenaline)	Retrospective review November 2002 – August 2005	Oklahoma, US EMS database Intervention group – 106 Non-intervention group - 85	No differences between groups in survival to ED (primary outcome), survival to 24 hours or survival to discharge (secondary outcomes)	/
Thrombolysis administration					
2008 Bottiger (8)	Intra-arrest thrombolysis (tenecteplase vs. placebo)	Double-blind multicentre RCT January 2004 – March 2006	66 EMS systems in Austria, Belgium, France, Germany, Italy, The Netherlands, Norway, Spain, Sweden and Switzerland Intervention group – 525 Non-intervention group – 525	ITT analysis: 30-day survival (primary outcome): 14.7% intervention vs. 17% standard treatment (p=0.36) No difference between groups in hospital admission; ROSC; 24-hour survival; survival to discharge and each category of neurological outcome by CPC (secondary outcomes) Early termination	/
2011 Renard (9)	Intra-arrest thrombolysis (alteplase 50 mg single bolus or tenecteplase 100 units/kg single bolus)	Case control study September 2005 – March 2007	44 physician-manned vehicles in Paris Intervention group – 107 Non-intervention group – 1154	Survival to hospital admission (primary outcome): AOR 1.7 95% CI: 1.09-2.68 In non-shockable subgroup OR 3.61 95% CI: 1.88-6.98. There was no association found in shockable subgroup	+

Overall, there is little evidence supporting the use of vasopressin. The only study (5) showing any results in favour of vasopressin was non-randomised and had internal validity issues. It may be that the degree of benefit of vasopressin use is dependent on factors not explored thoroughly in the current evidence, such as presenting rhythm, timing/prolongation of drug therapy and concomitant use with adrenaline. Further high level, rigorous studies are required before definitive conclusions can be drawn.

Thrombolysis administration

Two studies investigated the use of thrombolytic agents in the intra-arrest phase of cardiac arrest (8,9), a double blind RCT undertaken across 66 EMS systems in Europe (8) and a case-control study in Paris (9).

In the RCT (8), no significant results between groups were observed for any outcome measure. Multiple subgroup analyses were undertaken and of patients who received bystander CPR, significantly more patients in the non-thrombolysis group survived to 30 days. After almost 12 months of data collection, this study discontinued the enrolment of asystole patients, followed by full early termination a further 15 months later, due to statistical futility. Possible explanations for the lack of apparent effect include short response times, short intervals between collapse and study drug administration, lack of antithrombin/platelet agent and overall higher survival to hospital discharge rates when compared with previous similar studies. In contrast, acute myocardial infarction (AMI), rather than primary arrhythmia, pulmonary embolism (PE) or other cardiac cause, was the presumed aetiology in a larger proportion of the intervention group. The action of tenecteplase suggests it would have a more profound effect in AMI patients, which would increase the observed effect in favour of the intervention.

In the case-control study (9), significantly higher survival to hospital admission was reported. However, sub-group analyses showed that significant between group differences were only present in patients that were not shocked. Of note is that patients who were shocked were more likely to receive fibrinolysis. The lack of randomisation (physician dependant decision on administration) and broad non-specific inclusion criteria may have introduced selection bias and impacted on the reliability of these results, although this was addressed to some extent through propensity-based matching to select controls. A further limitation is the lack of consistency of the thrombolytic agent (alteplase or tenecteplase).

Overall, these studies provide little evidence in favour of the use of intra-arrest thrombolysis and have major limitations. Further studies addressing these limitations and specifics such as patient selection, timing and agent/s, are required to further inform the evidence base and future direction.

Discussion

Two strategies focussing on pharmaceuticals were identified for full review – administration of vasopressin and administration of thrombolysis. Neither of these strategies have any strong supportive evidence. Vasopressin and thrombolysis use in cardiac arrest patients in general (in-hospital as well as out-of-hospital) has been researched for some time, with no high-quality evidence for their benefit. Potentially, their use has benefit in specific patient subgroups, so although implementation of these strategies is not currently recommended from a general perspective, monitoring of the evidence base should definitely be continued.

In recent years, strategies to improve outcomes from OHCA have become more focussed on CPR quality and less on drug administration, so the findings of this review are largely unsurprising. Nevertheless, lack of rigour in conducting the studies is a possible explanation for lack of demonstrated effect. It is therefore essential that further, more rigorous studies are undertaken and the evidence base is monitored.

Limitations

There were several limitations of this systematic search and review. Although the review methodology was rigorous, it is possible that relevant studies may have been missed. Additionally, studies published in a non-English language or within grey literature only were not included. This was not a systematic review, so detailed critical appraisal of each included paper was not conducted (and was not feasible due to the broad objective of the review to include all relevant strategies). Nevertheless this may have strengthened the review.

Six studies were excluded from the review because there was only one study related to that strategy. Future research involving these strategies (passive oxygen insufflation, hypertonic saline administration, erythropoietin administration, lignocaine administration prophylactically, procainamide administration, and waveform analysis-guided shock timing) will further inform the evidence base, so should be monitored.

Conclusion

There is currently no strong evidence to support the introduction of vasopressin or thrombolysis administration in OHCA. The lack of evidence may in part be due to lack of rigour in conducting studies, or it may be that vasopressin or thrombolysis are advantageous for specific subsets of OHCA patients only. Therefore, future research should be rigorous in design and involve specific patient subsets.

Recommendations

- Future research into intra-arrest use of vasopressin or thrombolysis should be undertaken with rigorous design and investigation into different patient subsets.
- The evidence base for intra-arrest vasopressin, thrombolysis and other drugs should be monitored. There is a potential for the requirement of further investigation into the use of drugs specifically for OHCA if new scientifically plausible strategies are developed.
- Monitoring of the evidence base for other potential strategies outside the constraints (time or feasibility) of this review.

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Competing interests

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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SUPPLEMENTAL MATERIAL (PART A – PHARMACEUTICAL STRATEGIES) – Data supplement published online

Supplemental Table 1: Additional information for each identified study

Year and lead author	Limitations	Additional results	Other
Vasopressin administration			
2007 Mally (1)	• Adrenaline administration not consistent in cases – unsure if results are due to vasopressin alone or synergistic effect between vasopressin and adrenaline • No randomisation – allocation depended on year of incident and protocol changes (vasopressin was first line treatment in VF since Nov 2003 and in asystole since 2005) and availability of vasopressin. Controls were largely in the earlier years of the study. Strange that they knew at the beginning of the study that the protocols would change, otherwise not truly prospective • Limitations not discussed • In control group, sig higher doses adrenaline needed, longer CPR and more other drugs used (bicarbonate, atropine etc) ($p<0.05$) • Hospital discharge - Can assume no differences in shockable subgroup due to multivariate analysis although not strictly reported. PEA subgroup is unknown	In asystole subgroup higher hospital discharge rate in the intervention group ($p=0.04$) Neurological outcome of discharged patients was better (CPC 1 or 2) in the intervention group ($p=0.04$)	Included: 18 years+ non-traumatic, no terminal illness, no hypothermia (<30deg). No significant demographic differences. 40 units vasopressin every 3 minutes either with or without adrenaline. Non-intervention group - Adrenaline only every 3 mins.
2008 Gueugniaud (2)	• Enrolment only of subjects that required adrenaline (poor prognosis sample)	In PEA subgroup, survival to hospital discharge sig higher in controls	Included: 18 years+ non-traumatic only. Excluded: Terminal illness or pregnancy.

	• Low incidence of VF (the 'best' patients) compared to previous studies (increased use of AED in BLS in France before the study) • ITT principle applied for data analysis although patients who did not consent were excluded from analysis - Therefore not strictly applied • Significantly more men in cases • No standardisation of in-hospital care		Non-shockable rhythms underwent randomisation immediately, those in shockable rhythms underwent randomisation post 3 failed shocks. 2 doses of 40 units vasopressin alongside adrenaline, then adrenaline only.
2010 Cody (3)	• Not randomised • Small sample size – although power estimations indicated the study did meet adequate numbers • Retrospective nature • Insufficient number of survivors to report on neuro outcomes • Pre-hospital environment prevented efforts to control for variables such as pre-arrival CPR, response times, time to drug administration.	N/A	Included: 18 years+, non-traumatic only Adrenaline only for first 17 months then vasopressin given simultaneously with adrenaline during the final 17 months of study 1 dose of 40 units alongside adrenaline
Administration of thrombolysis			
2008 Bottiger (4)	• No antithrombin or antiplatelet agent may impact results (TNK increases platelet activation) • Short response intervals, short intervals between collapse and drug administration and higher than normal survival to discharge rates may prevent the attributable benefit of TNK being seen • Impossible to confirm the causes of underlying disease ie. confirm cardiac aetiology • Post resuscitation care not standardised • Bias in patient selection possible (do not know who could have been included)	Multiple subgroup analyses show benefit (primary outcome) only in controls who received bystander CPR. Multiple subgroup analyses undertaken	Included: Adult, presumed cardiac cause only with initiation of BLS within 10 mins of collapse. Excluded: Suspected non-cardiac cause, internal bleeding, neuro impair, coagulation disorders, pregnancy, in other clinical study, institutionalisation. Mobile intensive care unit (EMS vehicle with ACLS capability) dispatched, unknown staff level. Asystole and PEA randomised post IV access. VF/VT post 3 failed shocks.

	• Larger proportion of presumed aetiology of AMI (rather than primary arrhythmia, PE or other cardiac cause) in cases		Initial discontinuation of enrolment of asystolic patients. Trial terminated prematurely for futility after enrolling 1050 patients. No improvement.
2011 Renard (5)	• Physician selected patients received FT by criteria that were not clearly identified - May be due to suspicion of PE • Retrospective nature	Patients more likely to be a case if a shock was administered	Included: 18 years+ with non-traumatic. Propensity based matching to select controls.

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Review

Strategies to improve out-of-hospital cardiac arrest outcomes in the pre-hospital environment – Part B: non-pharmaceutical strategies

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Abstract

Introduction
Out-of-hospital cardiac arrest (OHCA) historically has low survival rates. Higher rates of survival have recently developed in some small geographical areas, which pre-empted an increase in the volume of research in this field. The aim of this paper is to consolidate the findings of the strategies that do not focus on drugs.

Methods
This is a systematic search and review, rather than a systematic review. A search of four databases (MEDLINE, CINAHL, Informit, Scopus) was undertaken in February 2017. Papers published between 2007 and 2017 containing strategies that may be used by paramedics when resuscitating adult patients in OHCA from presumed cardiac aetiology were identified.

Results
Twenty-eight studies were included in the review, comprising six separate strategies. This manuscript reports on the four non-pharmaceutical strategies (use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation and application of therapeutic hypothermia).

Conclusion
Use of a modified resuscitation protocol to improve the quality of cardiopulmonary resuscitation, was the only strategy showing evidence to warrant a recommendation for immediate implementation. Future studies should focus on strategy specific patient subsets.

Keywords:
heart arrest; emergency medical service; advanced life support

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Introduction

Globally, out-of-hospital cardiac arrest (OHCA) is a substantial problem with historically low survival rates (1). Impressively high rates of survival from OHCA have recently been reported in some small geographical areas, resulting in increased published research in this field. There are now many studies that have investigated specific strategies to improve outcomes, so it is timely this evidence is reviewed and consolidated.

The aim of this review is to identify, describe and synthesise the evidence for each strategy and make recommendations for improved outcomes from OHCA in high income countries with developed out-of-hospital health care. This is the second in a series of two papers arising from a systematic search and review investigating strategies to improve outcomes from OHCA. Part A addressed strategies focussing on pharmaceuticals (2), and this paper (Part B) addresses strategies focusing on non-pharmaceuticals.

Methods

This study is a systematic search and review (3) in which systematic methods were utilised for searching literature, data extraction, and appraising included studies. The focus is the component of emergency medical services (EMS) provided care which includes intra-arrest and immediate post-arrest life support. The full methods (search strategy, inclusion/exclusion criteria, data extraction, PRISMA diagram) and initial results have been reported previously (Part A) (2). Briefly, four databases (MEDLINE, CINAHL, Informit, Scopus) were searched systematically in February 2017. Papers published between 2007 and 2017 describing primary studies of strategies appropriate for use by paramedics when resuscitating adult patients in OHCA from presumed cardiac aetiology were identified.

Forest plots for each of the four strategy groups were constructed using Review Manager (RevMan) (version 5.3, Copenhagen). This was to provide a visual summary of results to assist with interpretation. The outcome was survival to hospital discharge, or survival to 30 days for studies that did not record survival to hospital discharge. An overall effect size was deliberately not calculated, as this was not meta-analyses and was not the intended purpose of the review. An intention to treat approach was used for randomised controlled studies (RCTs) and the equivalent for non-RCTs.

Results

Twenty-eight papers were included in the review, incorporating six groups of strategies. There were four groups of non-pharmaceutical strategies, which incorporated 23 studies (Table 1). Five papers relating to two pharmaceutical strategies have been reported previously in Part A (2).

Table 1. Strategies and number of papers in this review

Strategy	Number of studies
Use of a modified resuscitation protocol*	7
Use of a mechanical chest compression device	7
Intra-thoracic pressure regulation	3
Application of therapeutic hypothermia	6

*This group includes studies in which the modified resuscitation protocol was primarily aimed at improving CPR quality. This strategy was also known as minimally interrupted cardiac resuscitation, cardio-cerebral resuscitation, team-focussed CPR and pit crew approach.

The 23 studies included in this review are summarised in Table 2, grouped by the four strategies. The results of the studies are visually summarised using Forest Plots in Figure 1, also grouped by strategy.

Use of a modified resuscitation protocol

Modified resuscitation protocol (MRP) was investigated in seven studies (4-10), all aimed at actively improving the quality of the resuscitation attempt. Four studies (one large cluster-randomised trial (7) and three before/after study designs (4-6)) focused on reducing interruptions in chest compressions and three studies had a broader scope, involving a pit crew approach to resuscitation (all prospective, before/after designs (8-10)). Collectively, these seven studies suggest a MRP improves survival to hospital discharge (Figure 1).

Some common components of the four modified resuscitation protocols focussing on reducing interruptions in chest compressions (such as emphasis on the quality of chest compressions and delayed definitive airway placement) have already been implemented into current standard practice. However, the deviation from current practice among all four studies was a meaningful reduction in interruptions in chest compressions. This was applied in the RCT (7) by continuous chest compressions alongside concurrent ventilations; using an altered ratio of compressions to ventilations (50:2) in the study by Gaza et al (6); and initiating resuscitation with 200 uninterrupted compressions without ventilations in the remaining two studies (for three cycles in the Kellum et al study (5) and up to 8 minutes in the Bobrow et al study (4)). Reduction in positive pressure ventilations were observed in the three before/after studies (4-6). Bobrow et al used passive oxygen insufflation (4), whereas a change of ventilation pattern (at least in part), without a reduction in ventilations delivered overall, was observed in the RCT (7).

All three before/after studies (4-6) showed results in favour of the modified protocol. The effect size on survival to hospital discharge was more pronounced in the subgroup of witnessed shockable patients in the Bobrow et al (4) and Gaza et al (6) studies. Favourable results in this subgroup were consistent with the Kellum et al study (5). Significant favourable return of spontaneous circulation (ROSC) rates were shown in the Kansas City study (6) post-protocol implementation for the subset of witnessed shockable, however ROSC rates for all rhythms and witness status were not reported. No significant effects were observed on ROSC and survival to admission rates by Bobrow et al (4) but only 61% of cases treated after training actually met the complete MRP compliance criteria. When protocol compliance analysis was undertaken, ROSC and survival to admission rates became significantly favourable in those who received treatment with MRP compared to those who did not. Survival to hospital discharge rates also improved.

While the results of the three before/after studies are positive, interpretation must be considered within the context of limitations: 1) study design and differences in inclusion/exclusion criteria; and 2) multiple components within each protocol which may have impacted positively or negatively on patient outcomes. It is impossible to know how much impact was attributable to which change. Compliance analysis was

Study or Subgroup	MRP Events	MRP Total	No MRP Events	No MRP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bobrow 2008	36	668	4	218	0.4%	2.94 [1.06, 8.16]
Kellum 2008	42	89	18	92	1.1%	2.41 [1.51, 3.86]
Garza 2009	47	339	82	1097	2.3%	1.85 [1.32, 2.60]
Nichol 2015	1129	12613	1072	11035	67.9%	0.92 [0.85, 1.00]
Bobrow 2013	35	252	20	232	1.2%	1.61 [0.96, 2.71]
Hopkins 2016	71	407	36	330	2.4%	1.60 [1.10, 2.32]
Pearson 2016	1166	10104	292	4025	24.8%	1.59 [1.41, 1.80]
Total events	2526		1524			

Heterogeneity: Chi² = 81.76, df = 6 (P < 0.00001); I² = 93%
Test for overall effect: Z = 4.53 (P < 0.00001)

Study or Subgroup	MCC Events	MCC Total	No MCC Events	No MCC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jennings 2012	2	66	15	220	1.1%	0.44 [0.10, 1.89]
Wik 2014	233	2099	196	2132	31.1%	1.21 [1.01, 1.45]
Smekal 2011	6	75	7	73	1.1%	0.83 [0.29, 2.36]
*Axelsson 2013	126	1183	86	1218	13.6%	1.51 [1.16, 1.96]
Rubertsson 2014	117	1300	118	1289	19.0%	0.98 [0.77, 1.25]
*Perkins 2015	104	1652	193	2819	22.8%	0.92 [0.73, 1.16]
Zeiner 2015	36	283	117	655	11.3%	0.71 [0.50, 1.01]
Total events	624		732			

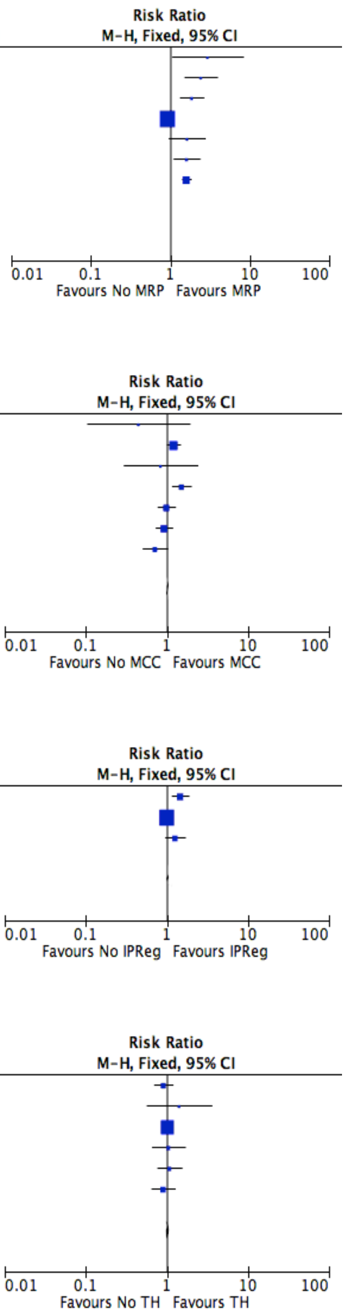
Heterogeneity: Chi² = 17.37, df = 6 (P = 0.008); I² = 65%
Test for overall effect: Z = 1.29 (P = 0.20)

Study or Subgroup	IPReg Events	IPReg Total	No IPReg Events	No IPReg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aufderheide 2008	238	1750	86	920	20.5%	1.45 [1.15, 1.84]
Aufderheide 2011a	357	4373	355	4345	64.7%	1.00 [0.87, 1.15]
Aufderheide 2011b	104	840	80	813	14.8%	1.26 [0.96, 1.66]
Total events	699		521			

Heterogeneity: Chi² = 8.03, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 2.19 (P = 0.03)

Study or Subgroup	TH Events	TH Total	No TH Events	No TH Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bernard 2010	56	118	61	116	13.6%	0.90 [0.70, 1.17]
Bernard 2012	10	82	7	81	1.6%	1.41 [0.56, 3.53]
Kim 2014	259	688	249	671	55.9%	1.01 [0.88, 1.16]
Garrett 2011	26	208	40	334	6.8%	1.04 [0.66, 1.66]
Schenfeld 2015	43	80	26	52	7.0%	1.07 [0.77, 1.51]
Bernard 2016	63	618	66	580	15.1%	0.90 [0.65, 1.24]
Total events	457		449			

Heterogeneity: Chi² = 1.83, df = 5 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)



*The outcome displayed is survival to 30 days
Modified resuscitation protocol (MRP), use of a mechanical chest compression device (MCC), intra-thoracic pressure regulation (IPReg) and application of therapeutic hypothermia (TH).

Figure 1. Forest Plot of survival to hospital discharge after OHCA, by pre-hospital strategy (non-pharmaceutical)

undertaken only in one study (4), we cannot be sure how closely the protocols were followed in the others. Additionally, the training conducted would likely have improved other areas of care, so it is difficult to assess the impact on outcomes. The cluster-randomised trial (7) observed slightly lower rates of survival to hospital discharge with favourable neurological outcomes in the intervention group compared with the control group, but these differences were not significant. The only significant difference in favour of the intervention group was in the outcome of hospital free days (number of days out of hospital up to 30 days post-event). In compliance-only analyses, survival was also lower in the intervention group ($p<0.001$). A large proportion of the compliance only population were excluded as the algorithm used could not differentiate between intervention and control groups, leaving imbalances in characteristics and treatments between groups. This and the multiple other limitations may provide some explanation for the results.

The remaining three studies in this group involved a pit crew approach (8-10). The principles of pit crew approach include many factors already included within current EMS CPR training in Australia, such as attention to correct compression rate, rhythm, depth, recoil, limiting interruptions and rotating compression providers regularly. However, pit crew approach takes these concepts and applies them with a well-practiced choreographed approach. EMS providers have designated roles which are frequently practised within teams, so on treating a real OHCA patient, the process is smooth, organised and strictly structured, optimising efficiency.

The inclusion criteria for all three studies was patients who had an OHCA of non-traumatic aetiology and had a resuscitation attempt by EMS. The Pearson and Bobrow studies (8,10) further stipulated presumed cardiac aetiology, while the Hopkins study (9) excluded aetiologies of drowning and strangulation (in addition to trauma). The Hopkins study (9) included patients of all ages versus adults only in the Pearson and Bobrow studies (8,10).

Increased neurologically intact survival to discharge was shown in all three studies in the post-intervention group (8-10). Increased survival to hospital admission in the post-intervention phase was also demonstrated in all three studies, but was non-significant in the Pearson study (10). Additionally, the Hopkins study (9) showed increased field ROSC post-intervention and the Pearson study (10) demonstrated significant results in favour of the intervention in the subgroup of witnessed shockable cases (over all outcomes).

All three studies were retrospective and non-randomised. Individual components of the broader initiative studies (Hopkins and Bobrow (8,9)) cannot be analysed independently, so the true contribution of pit crew approach is uncertain. Additionally, it is difficult if not impossible to ascertain which components (or combination of) are effectively transferable to other areas/ organisations. The multiple agency contribution (with unknown consistency) of the study by Pearson (10) brings further limitations.

Overall, these seven studies provide some evidence that use of a modified resuscitation protocol (largely to improve the quality of CPR) will likely improve patient outcomes. The specifics of the strategies applied is inconsistent between studies, so the most effective application is still unclear, although all studies featuring a pit crew approach showed favourable outcomes. The studies with results in favour of the intervention are retrospective in nature and the only prospective randomised study (study without pit crew approach) showed no effect (7). Overall, results surrounding this strategy are promising but require further rigorous research.

Use of a mechanical chest compression device

Seven studies investigated use of a mechanical chest compression device (11-17). Two types of devices were found: 1) A load distributing band (LDB) design (Autopulse®); and 2) an active compression/decompression design (LUCAS). As shown in Figure 1, no consistent results were observed across studies in relation to the effect of mechanical chest compression devices on survival to hospital discharge/30 days.

Two studies involved a LDB device; one RCT (12) and one retrospective matched case-control study (11). The RCT showed no significant difference between groups in survival to hospital discharge with MRS<3, however significant reductions in ROSC to ED and survival to 24 hours were observed (12). Only some covariates were adjusted for in analyses, hence there are potentially other confounders that were not investigated. In the case-control study (11), ROSC to ED was higher in cases than controls but not significantly. Similar results were found within sub-analysis of bystander witnessed cardiac aetiology patients only and when data were stratified by shockable status.

Four studies (three RCTs (13,15,16) and one retrospective case series (14)) investigated the use of a LUCAS device. Two of the RCTs were large randomised trials (LINC (15) and PARAMEDIC (16)) and one was a smaller study (13) which acted as the pilot study for LINC.

There were some differences in the protocols applied with LUCAS in the RCTs. In the LINC study (15), 3-minute cycles of continuous compressions were applied to cases (with a shock delivered to all patients at the 90-second mark on the first round and shock delivered on subsequent rounds if shockable on last analysis), while controls received standard 2 minute cycles at 30:2. In the PARAMEDIC study (16), the same standard 2 minute cycles were applied to cases and controls. Factors such as continuous compressions and defibrillation during CPR are under investigation as strategies to improve outcomes in their own right and as a result, the impact of these cannot be ruled out as contributory to any findings in LINC (rather than solely the LUCAS).

All three studies investigated various length of patient outcome and all applied intention-to-treat (ITT) methodology. The pilot study was used to inform LINC, hence the relatively small sample, which is the likely explanation for the lack of significant results. No significant differences were found between the intervention and non-intervention groups for any outcome in LINC. This was also mostly true in PARAMEDIC, with exceptions of significantly fewer cases with favourable neurological outcome at 3 months (overall) and 30-day survival (shockable subset only). Compliant average causal effect analyses showed similar results.

In LINC (15), the lack of effect may have been due to the treatment differences between the intervention and non-intervention algorithms, which may have had a pronounced effect on survival (27). This is not the case in PARAMEDIC, but the pragmatic methodology likely explains the marginal results in favour of the control group. True adherence to algorithms and CPR quality were not routinely measured in any of the studies and there is some evidence of omission which may also impact observed outcomes.

The final study using LUCAS compared two time periods, before and after the introduction of LUCAS as part of ambulance equipment (14). There were significant increases in survival to admission between periods 1 and 2, however these improvements may be attributable to other factors (eg. implementation of the 2005 resuscitation guidelines and significant changes in witnessed status and proportions of patients receiving post-resuscitation care and bystander CPR). Further analysis indicated that among patients from period 2 only, survival to hospital was significantly lower in patients that had a LUCAS applied (n=705) versus those that did not (n=465). In multivariate analyses, administration of mechanical compressions was inversely associated with survival. This may be because the LUCAS device is only indicated in a high-risk cohort of patients, ie. those where initial manual CPR and defibrillation has been unsuccessful, much the same as adrenaline which was also inversely associated with survival in the same multivariate analysis. Testing strategies on high risk cohorts makes it difficult to provide a large enough sample to provide adequate power and is a problem with research involving many cardiac arrest strategies.

The final study involved both the Autopulse and LUCAS devices (17). Significantly lower rates of 30-day survival with favourable neurological outcome and sustained ROSC were found in the intervention group. A lower rate of survival to 30 days was also found in the intervention group, although non-significant. Additionally, when survival analysis adjusting for relevant variables was undertaken, use of a mechanical chest compression device was significantly associated with death in hospital. There were many limitations in this study most of which would likely yield results in favour of the intervention group, so the significant results against the intervention seem obscure.

Across all seven studies, there is insufficient rigorous evidence to support use of a mechanical chest compression device versus high quality manual CPR. There are some clear practical advantages of mechanical chest compression devices over manual compressions, such as the provision of continuous high-quality CPR without fatigue or inconsistencies which can remain uninterrupted throughout defibrillation and transport. It may be that further, more rigorous research could highlight true benefit to patient outcomes from their use in specific circumstances.

Intra-thoracic pressure regulation

Three studies (all led by the same author - Aufderheide) involved the use of single or multiple devices to regulate intra-thoracic pressure in the intra-arrest phase of cardiac arrest (18-20). Overall, no consistent trends were observed to suggest regulation of intra-thoracic pressure increases survival to hospital discharge (Figure 1).

Two of the studies were large multicentre RCTs, ROC PRIMED (19) and ResQTrial (20). In ROC PRIMED, there were no significant differences between groups for any outcome measure and the study was terminated early due to interim analysis demonstrating futility. On post-hoc analysis, increased survival to discharge with satisfactory neurological function was observed in the subgroup of patients who were in the second lowest quartile (59.9-71%), when defined by CPR fraction. ROC PRIMED had many limitations, which may have contributed to the lack of significant findings and early termination.

In ResQTrial, there were significant differences in favour of the intervention in survival to hospital discharge with MRS ≤3, survival to 90 days and survival to 1 year, but not in survival to 24 hours. There were some methodological issues with this study including early discontinuation of a third arm investigating the use of an Impedance Threshold Device (ITD) alone (without active compression-decompression cardiopulmonary resuscitation (ACDCPR)). It therefore cannot be established if the results are from either intervention independently or a synergistic effect of the two. This study appears methodologically sound, but the overall impact of the methodological and other limitations on results is largely unknown.

The third study compared two time periods before and after the introduction of the 2005 CPR guidelines, which included the use of an ITD (18). However, a major limitation of this study is that it is the human component of a larger study involving swine and effects cannot be solely attributed to the use of an ITD but may be a combination of interventions and guideline changes. When broken down by initial rhythm, survival to hospital discharge was significant only in cases of VF and was not significant in asystole or PEA.

There is some evidence supporting improvements in short term outcomes when an ITD is used in combination with ACDCPR and perhaps in survival to discharge in patients with an initial rhythm of ventricular fibrillation (VF) when ITD is used alone. There are profound limitations of the three studies in this review including funding/affiliations from the only current manufacturer of the ITD. To improve the evidence base in order to make a more definitive conclusion, large scale independent blinded RCTs isolating the ITD are required.

Application of therapeutic hypothermia
Six studies investigated therapeutic hypothermia (TH) (21-26), initiated in the post-arrest phase in three of the studies (21-23), in the intra-arrest phase in two (24, 26) and in either phase in one (25). None of these studies reported significant findings in survival to hospital discharge to support or refute therapeutic hypothermia (Figure 1).

All three studies where TH was initiated post-arrest were RCTs and used an IV infusion of cold fluid as the cooling method (21-23). The largest of these (23) used normal saline as the fluid. The patient outcome measures were analysed overall and stratified by initial VF status. Additionally, there were multiple limitations.

The remaining two studies (21,22) in which the strategy was initiated in the post-arrest phase were run concurrently, by the same research team and within the same population. One investigated patients with an initial rhythm of VF and a presumed cardiac aetiology only, for which a rapid infusion of 2 litres of lactated ringers was administered (21); the other included patients with an initial rhythm of asystole or pulseless electrical activity (PEA) of any aetiology and used 2 litres of Hartmann's (22). Therefore, these two studies collaboratively included all OHCA patients in this area for the specified time period, unless the initial rhythm was pulseless VT or other exclusion criteria were met.

The study investigating lactated ringers in VF (21), demonstrated no significant differences between groups in patient outcome measures so was stopped early due to perceived futility. This meant the parallel trial (22) was logistically too difficult to continue so was also stopped. While there were between group differences in favourable outcomes in the subgroup of cardiac aetiology only, these were not significant, however this may be due to limited sample size (and the early termination). There were further limitations to both studies.

Both studies in which TH was initiated in the intra-arrest phase of arrest used an infusion of cold normal saline (up to 2 litres) as the cooling agent; one of which was an RCT (26) and one was a before/after study (24). The RCT included adults of non-traumatic aetiology only, had high quality randomisation techniques and used ITT analysis (26). ROSC was investigated stratified by shockable status and occurred less frequently in the intervention group of those with an initially shockable rhythm, which remained when adjustments were made for fluid volume administered. This study was finished early due to a change in hospital cooling protocols, although significant results would have been unlikely. Additionally, only 10% of all cardiac arrest patients were enrolled, the reasons for which are unknown.

In the before/after study (24), higher rates of prehospital ROSC and survival to hospital admission were observed in cases than controls (only significant in pre-hospital ROSC). A positive linear association was also observed between the amount of cold fluid administered and likelihood of obtaining ROSC, with two significant changes in outcome at 200 mL (vs. ≤50 mL) and 700 mL (vs.≤200 mL). There were various limitations in addition to those associated with the retrospective nature of the study.

The remaining study initiated therapeutic hypothermia in either the intra or post-arrest phase (25). A therapeutic hypothermia protocol was implemented part way through the study period; providing the basis of a before/after study. The primary outcome was time to target temperature following ROSC while the patient specific outcomes were secondary. There were no significant differences between groups in any of the outcomes, which for patient specific outcomes is likely the result of insufficient power. Additionally, there were other limitations to this study.

Overall, there is a lack of strong evidence supporting the implementation of TH in either the intra-arrest or post-arrest phase of out-of-hospital cardiac arrest. The only study (24) showing any significant results in favour of out-of-hospital TH in either phase was a less rigorous study with many inherent limitations. The studies of more rigorous design finished early. In addition, the specifics of the strategy such as cooling method, fluid type and patient selection also require clarification.

Discussion

Four non-pharmaceutical strategies were identified for inclusion in this systematic search and review. The most positive results were observed for use of a modified resuscitation protocol, particularly use of a pit crew approach. The modified resuscitation protocols differed but were common in their primary objective of improving the quality of CPR. Instigation of such protocols aims to support paramedic skills and ensure the delivery of higher quality CPR will not suffer over time, as would be expected if paramedics simply received training with no surrounding governance.

Quality CPR makes a difference to outcomes (28). As such, recent literature has a heavy focus on the importance of achieving optimal CPR (28-34) and therefore, it is unsurprising that studies identified in this review with protocols promoting and maintaining optimal CPR, showed positive results. There has also been recent focus on optimising the use of factors promoting the efficiency of teams in clinical circumstances, such as leadership and the use of non-technical skills, to improve outcomes (35, 36). A pivotal study to this concept in the out-of-hospital environment was TOPCAT2 (37), which presented a specialist second-tier response to OHCA to focus on non-technical skills (more specifically leadership, communication and clinical decision making), with goals closely aligned to that of a pit crew approach. A primary objective of a pit crew approach is to promote and support the deliverance of high quality CPR, but there is little evidence specifically investigating further benefits. The Bobrow study (8) measured minimally interrupted cardiac resuscitation protocol (MICR) compliance. There was an increase in compliance in the post-intervention phase, supporting the importance of the delivery of high-quality CPR. Additionally, when calculations including adjustments for MICR protocol compliance were undertaken (so effectively removing the impact of CPR quality from the intervention), the results remained significantly in favour of the intervention, indicating there may be benefit from additional constituents of the intervention. This suggests factors of a pit crew approach (such as highly effective teamwork and impeccable use of non-technical skills) impact positively on the quality of a resuscitation attempt beyond their contribution to the provision of high-quality CPR.

Equivocal results were independently found for use of a mechanical chest compression device and intra-thoracic pressure regulation, meaning that neither can be recommended for routine implementation.

There are four recent systematic reviews/meta-analyses on use of a mechanical chest compression device, three of which (38-40) support the findings presented in this systematic search and review (to not recommend for routine implementation). The other (a meta-analysis) contradicts the findings of this study, concluding that LDB CPR had significantly greater odds of ROSC than manual CPR (1.62; 95% CI: 1.36-1.92; $p<0.001$).

Use of a mechanical chest compression device does have clear practical advantages in certain subsets of patients, such as those requiring transport. There have been recent international studies investigating the use of a mechanical chest compression device, specifically to facilitate high quality chest compressions during transport in subsets of patients that may benefit from more definitive care, such as interventional cardiology and/or extracorporeal membrane oxygenation (ECMO) (41,42). Some international ambulance services (such as London) already have such procedures in place for transfer to interventional cardiology only, but there are none yet routinely in place for direct transfer specifically to ECMO. The relevant ECMO studies to date have hypothesis generating capability only, but with positive results, hence require more rigorous investigation. Additionally and more recently, use of a mechanical chest compression device as a pre-empt to out-of-hospital initiated ECMO is a further strategy which has been investigated in a hypothesis generating capacity (43), which will likely lead to more rigorous studies.

Three studies in this review investigated a method of regulating intra-thoracic pressure. The theory of intrathoracic pressure regulation to improve outcomes is certainly convincing, but the inherent floors in the three reviewed studies limit interpretability. Therefore, more rigorous evidence, with potential strategy development, is required before a recommendation can confidently be made. An alternative method of intrathoracic pressure regulation is use of a device which regulates pressure. No study using this device (known as CirQlator) (45), fulfilled the inclusion criteria for this review, so it was not discussed. Further investigation of alternative methods to regulate intrathoracic pressure such as this, would contribute to the evidence base of this strategy.

In this review, there was no supportive evidence in favour of the application of out-of-hospital therapeutic hypothermia. For some time, therapeutic hypothermia in the post-cardiac arrest patient has been recognised as a beneficial treatment (as supported by a recent systematic review and meta-analysis (46)) and routinely applied to in-hospital protocols where feasible. The benefits of the out-of-hospital application of this strategy has been under greater question; although out-of-hospital application has been shown to achieve optimal temperature earlier than in-hospital application, longer term benefits have not been proven (47). Additionally, the timing (intra-arrest or post-arrest) and method of out-of-hospital application has also been questioned. The cooling methods in the studies identified by this review are the administration of various types of cold fluid (normal saline, lactated ringers or Hartmann's). However, there are other feasible out-of-hospital cooling methods used either in combination or isolation within published literature that did not meet the inclusion criteria for this review. Examples are external cooling measures such as the application of ice-packs and use of an intra-nasal cooling device known as Rhinochill (48-50). Preferential timing and method are important questions to answer before a recommendation could be made.

Additionally, recent high quality in-hospital studies have suggested that temperature maintenance, rather than reduction is the important factor to achieve preferred patient outcomes (51). Although outside the inclusion boundaries of this review, this brings further question to the value and/or specifics of a out-of-hospital strategy and it seems logical that further out-of-hospital studies be informed by this and further evidence, including in-hospital studies.

The limitations of this search and review have been reported previously (2). Limitations include the exclusion of studies published in a non-English language or in grey literature, the potential that relevant studies were missed (although the methodology was rigorous) and the lack of detailed critical appraisal for each paper due to the broad objective and design of the review. While Forest plots were used to visually summarise results of included studies, no overall effect was presented. This was deliberate as this was not meta-analyses. The inherent differences between studies would make an overall effect size misleading; nonetheless, this is acknowledged as a limitation. Recommendations arising from this review are summarised in Table 3.

Table 3. Recommendations

1	Where feasible, a modified resuscitation protocol to achieve high quality CPR (preferably with some degree of pit crew approach) be implemented in EMS internationally. Systems in which this is implemented should have established sophisticated data collection methods in place to allow the measurement of impacts over time
2	Further research into the use of a mechanical chest compression device be undertaken with a focus on specific subsets of OHCA patients. The most beneficial approach is likely in collaboration with other strategies, to provide a pathway to more definitive care. With no further research and where feasible, mechanical chest compression devices should be introduced for circumstances where clear practical advantages exist, ie. single paramedic response, prolonged resuscitation and/or requirement of intra-arrest transport
3	Large independent studies of intra-thoracic pressure regulation effectiveness be commenced
4	Further research into out-of-hospital therapeutic hypothermia with particular consideration of timing (intra-arrest versus post-arrest) and method of application
5	Large epidemiological studies be undertaken to inform target populations

Conclusion

There is a shortage of high-quality evidence for strategies that may be used by paramedics to improve outcomes from OHCA. The only strategy group that showed adequate evidence to warrant immediate implementation recommendations was use of a modified resuscitation protocol to improve the quality of CPR (preferably with some degree of pit crew approach).

Many strategies are likely advantageous for specific subsets of OHCA patients, so it may be beneficial that future research involving specific strategies focus on those subsets.

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Conflict of interest

The authors declare they have no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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Table 2. Evidence table for non-pharmaceutical strategies to improve OHCA outcomes in the out-of-hospital environment

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a modified resuscitation protocol					
2008 Bobrow (4)	Minimally interrupted cardiac resuscitation (MICR)	Before/after study: Before data Jan 2005 – June 2005 After data July 2005 onward (as training implemented at the site) – June 2007 Protocol compliance analysis (PCA) – Those who received MICR Jan 2005 – Nov 2007 (not ITT)	Arizona, US ITT analysis: Before – 668 After – 218 PCA analysis: Before – 1799 After – 661	Before/after analysis: Survival to discharge (primary outcome): 1.8% before vs. 5.4% after (OR=3.0; 95% CI: 1.1-8.9). In witnessed shockable subgroup: (174) 4.7% before vs. 17.6% after (OR=8.6; 95% CI: 1.8-42) ROSC (secondary outcome): 15.6% before vs. 23.1% after (OR=1.3; 95% CI: 0.8-2.0) Survival to admission (secondary outcome): 16.1% before vs. 16.9% after (OR=0.8; 95% CI: 0.5-1.2)	+
2008 Kellum (5)	Cardio-cerebral resuscitation	Before / after study Before: Jan 2001 – Dec 2003 After: mid 2004 – mid 2007	Wisconsin, US Protocol introduced in 2004 staggered approach of four EMS regions ITT analysis: Before – 92 After - 89	Before/after analysis: Survived to discharge (primary outcome): 18/92 (20%) before vs. 42/89 (47%) after (95% CI: 0.1-0.4) Survived neurologically intact (CPC of 1) (secondary outcome): before 14/92 (15%) vs. 35/89 (39%) after (95% CI: 0.1-0.4)	+
2009 Garza (6)	Modified resuscitation protocol (MRP)	Before / after study Before: Jan 2003 - March 2006 After: April 2006 - March 2007	Kansas City, US – uses first responders from the KCMO fire dep ITT analysis: Before - All rhythms 1097; subgroup bystander witnessed shockable (main study) 143 After - All rhythms 339; subgroup bystander witnessed shockable (main study) 57	Before/after analysis: Survival to discharge (primary outcome): 7.5% before vs. 13.9% after p<0.001. In witnessed shockable subgroup 22.4% before vs. 43.9% after (p=0.0024; OR 2.71; 95% CI 1.34-5.49) ROSC (secondary outcome): 37.8% before vs. 59.6% after (p=0.0051; OR 2.44; 95% CI 1.24-4.80)	+
2015 Nichol (7)	Continuous chest compressions	Cluster randomisation with crossover (47 clusters of EMS agencies – twice per year clusters were crossed over to the other strategy) First agency entered run in phase 6 June 2011 – all study sites stopped 28 May 2015	Resus outcomes consortium (ROC) – Network which includes 10 clinical sites in North America, the regional EMS agencies, 8 ROC sites and 114 EMS agencies ITT analysis: Intervention group: 12,613 Non-intervention group (CPR given at ratio 30:2): 11,035 Compliance analysis (referred to as per-protocol population within study): Intervention group: 6529 Non-intervention group: 3678	ITT analysis: Survived to discharge (primary outcome): 9% intervention vs. 9.7% non-intervention (p=0.07) Survived to discharge with favourable neurological outcome (MRS [illegible]3) (secondary outcome): 7% intervention vs. 7.7% non-intervention group (p=0.09)	/

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a modified resuscitation protocol					
2013 Bobrow (8)	Multiple interventions – MICR with pit crew model and real-time audio-visual feedback	Before / after observational cohort study Before (phase 1): 7th Oct 2008 – 31st March 2010 After (phase 2): 27th May 2010 – Sep 2011	Mesa, Arizona, US Single fire-based EMS agency Before - 232 After - 252	Survival to hospital discharge (primary outcome): 8.7% before vs. 13.9% after (OR 1.73; 95% CI 0.93 – 3.21) and (AOR 2.72; 95% CI 1.15 – 6.41) Favourable functional outcome at discharge (CPC score of 1 or 2) (secondary outcome): 6.5% before vs. 10.8% after (OR 1.76; 95% CI 0.88 – 3.52) and (AOR 2.69; 95% CI 1.04 – 6.94)	+
2016 Hopkins (9)	Multiple interventions - Various CPR quality improvement initiatives eg. real-time CPR feedback technology, post-incident feedback, rhythm filtering technology, passive O2 option, impedance threshold device (ITD) added in July 2013, simplified medication algorithm, pit crew approach and more appropriate transport destinations	Before / after study Before: 1 Sep 2008 – 30 Sep 2011 After: 1 Oct 2011 – 31 Dec 2014 Strategy implemented in Sep 2011	Salt Lake City, US Internal Utstein style database ITT analysis: Before – 330 After - 407	Neurologically intact (CPC 1 or 2) survivors at discharge (primary outcome): 25/330 = 8% before vs. 65/407 = 16% after. Increase between periods was 8.4% (p=0.0005; 95% CI 3.8 – 13) Field ROSC (secondary outcome): 100/330 = 30% before vs. 179/407 = 44% after (p<0.0001) Survival to hospital admission (secondary outcome): higher in the after group but not significantly	+
2016 Pearson (10)	Team focussed CPR (TFCPR) (also known as high performance CPR/ pit crew approach)	Before / after observational cohort study Jan 2010 – June 2014 State-wide protocol introduced in July 2012 but incorporation of TFCPR began in 2011	North Carolina, US North Carolina EMS agencies reporting to CARES database Before – 4,025 After – 10,104 Total sample for logistic regression is 11,232 (due to other missing variables)	Neurologically intact at discharge (CPC 1 or 2) (primary outcome): 193/4025 = 4.8% before (95% CI 4.2-5.5) vs. 836/10104 = 8.3% after (95% CI 7.7-8.8) (significantly higher) Survival to hospital admission (secondary outcome): 21.1% before vs. 27.2% after (significantly higher by 95% CI) Survival to hospital discharge (secondary outcome): 7.3% before vs. 11.5% after (significantly higher by 95% CI) In witnessed shockable subgroup, all outcomes significantly higher after: Neurologically intact at discharge 16.8% vs. 28.9%; survival to hospital admission 42.7% vs. 54.1%; survival to hospital discharge 22.1% vs. 36.6%	+

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
Use of a mechanical chest compression device					
2012 Jennings (11)	Load distributing band (LDB) (Autopulse®)	Case-control study 1 October 2006 – 30 April 2010	Victoria, Australia Cases - 66 Controls (manual CPR) - 220	Survival to hospital (primary outcome): 17/66 (26%) cases vs. 43/220 (20%) controls (AOR 1.69; 95% CI 0.79-3.63). In shockable subgroup: 50% cases vs. 33% controls (p=0.2). In non-shockable subgroup: 19% cases vs. 12% controls (p=0.28). In bystander witnessed cardiac aetiology subgroup: 14/48 (29%) cases vs. 21/116 (18%) controls (AOR 1.80; 95% CI 0.78-4.11) Survival to discharge (secondary outcome): 2/66 (3%) cases v 15/220 (7%) controls (p=0.38).	/
2014 Wik (12) CIRC	Load distributing band LDB (Autopulse®)	Sequential multicentre RCT March 2009 – Jan 2011	Three US and two EU sites Intervention group: 2099 Non-intervention group (manual CPR) - 2132	Survival to hospital discharge (primary outcome): 9.4% intervention vs. 11% non-intervention (AOR 0.89; 95% CI 0.72-1.1) ROSC to ED (secondary outcome): 28.6% intervention vs. 32.3% non-intervention (AOR 0.84; 95% CI 0.73-0.96) 24hr survival (secondary outcome): 21.8% intervention vs. 25% non-intervention (AOR 0.86; 95% CI 0.74-0.998) Discharged with a MRS≤3 (secondary outcome): OR 0.8; 95% CI 0.47-1.37	/
2011 Smekal (13) LINC pilot	Active compression-decompression CPR (ACDCPR) (LUCAS)	RCT pilot study Feb 2005 – April 2007	Sweden ITT analysis: Intervention group - 75 Non-intervention group (manual CPR) - 73	ROSC with BP above 80/50 for at least 5 mins (primary outcome): 23/75 intervention vs. 19/73 non-intervention group (p=0.59) ROSC (secondary outcome): 30/75 intervention vs. 23/73 non-intervention (p=0.3) Hospitalised alive >4h (secondary outcome): 18/75 intervention group vs. 15/73 non-intervention group (p=0.69) Discharged alive (secondary outcome): 6/75 intervention vs. 7/73 non-intervention (p=0.78)	/
2013 Axelsson (14)	ACDCPR (LUCAS)	Before / after study Before (period 1): Jan 1998 – May 2003 After (period 2): Nov 2007 – Dec 2011 Interim period not used due to another study and transition of the OHCA registry.	Gothenburg, Sweden Swedish OHCA registry ITT analysis: Before - 1218 After - 1183 Compliance analysis (main analysis, period 2 only): Intervention – 705 (60%) Non-intervention - 465 (39%) Unknown – 13 (1%)	ITT analysis: Survival to hospital admission (primary outcome): 25.4% before vs. 31.9% after (p<0.0001); survival to 1 month (secondary outcome): 7.1% before vs. 10.7% after (p<0.002) Compliance analysis: intervention vs. non-intervention admitted alive to hospital 28.6% vs. 36.1% (p=0.008) and survival to 1 month 5.6% vs. 17.6% (p<0.0001) respectively	Period 1 v period 2: + Period 2 only: /

Year and lead author	Strategy details	Study design/ timeframe	Setting/recruiting method and sample size	Main results	Type of association
2014 Rubertsson (15) LINC	ACDCPR (LUCAS)	Multicentre RCT Jan 2008 – Aug 2012	Sweden, Netherlands and the UK Intervention group - 1300 Non-intervention group (manual CPR) - 1289	4-hour survival (primary outcome): 23.6% intervention vs. 23.7% non-intervention Survival to ICU discharge with CPC 1 or 2 (secondary outcome): 7.5% intervention vs. 6.4% non-intervention Hospital discharge with CPC 1 or 2 (secondary outcome): 8.3% intervention vs. 7.8% non-intervention 1-month survival (secondary outcome): 8.1% intervention vs. 7.3% non-intervention 6-month survival (secondary outcome): 8.5% intervention vs. 7.6% non-intervention No significant difference between groups in any outcome	/
2015 Perkins (16) PARAMEDIC	ACDCPR (LUCAS2)	Cluster randomised (by vehicle) trial 15 April 2010 – 10 June 2013	Four UK ambulance services Data collected by individual ambulance services and submitted to central trial database Intervention group - 1652 Non-intervention group (manual CPR) – 2819	Survival at 30 days post arrest (primary outcome): 104/1652 = 6% intervention vs. 193/2819 = 7% non-intervention (non-significant in OR and AOR) ROSC, survival to admission and survival at 3 months (secondary outcomes) were very similar between groups Favourable neurological outcome at 3 months (CPC 1 or 2) (secondary outcome) lower in intervention group (AOR 0.72; 95% CI 0.52-0.99)	/
2015 Zeiner (17)	LDB (Autopulse®) or ACDCPR (LUCAS)	Non-randomised trial July 2013 – Aug 2014	Vienna, Austria Intervention group - 283 Non-intervention group (manual CPR) - 655	30-day survival with favourable neuro outcome (primary outcome): 56.8% intervention vs. 78.6% non-intervention group (p=0.009) Sustained ROSC (secondary outcome): 22.9% intervention vs. 30.7% non-intervention (p=0.017) Survival to discharge (secondary outcome): 12.7% intervention vs. 17.8% non-intervention (p=0.052)	/
Intra-thoracic pressure regulation					
2008 Aufderheide (18)	2005 American Heart Association CPR guidelines including ITD	Before / after study Dates of data collection not stated	Six EMS systems in the US Before - 1750 After - 920	Survival to hospital discharge (primary outcome): 9.3% before vs. 13.6% after (p=0.0008; OR 1.54; 95% CI 1.19-1.99). In VF subgroup, 18% before vs. 28.5% after (p=0.0008). No significant differences between groups in non-shockable subgroups	+
2011a Aufderheide (19) ROC Primed	ITD	Double blind RCT June 2007 – Nov 2009	10 sites in the US and Canada Intervention group - 4373 Non-intervention group (sham ITD) - 4345	No significant differences between groups in survival to discharge with MRS≤3 (primary outcome), ROSC on ED arrival, survival to admission, survival to discharge (secondary outcomes) Early termination	/
2011b Aufderheide (20) ResQtrial	ITD and ACDCPR	RCT Run in phase Oct 2005 – April 2009 Enrolled study March 2006 – July 2009	46 EMS agencies in US Intervention group: 840 Non-intervention group: 813	Survival to hospital discharge with MRS≤3 (primary outcome): p=0.019; OR 1.58; 95% CI 1.07-2.36 Survival to 90 days (secondary outcome): 10% intervention vs. 7% non-intervention (p=0.029) Survival to 1 year (secondary outcome): 9% intervention vs. 6% non-intervention (p=0.03)	+

Year and lead author	Strategy details	Study design/timeframe	Setting/recruiting method and sample size	Main results	Type of association
Application of therapeutic hypothermia					
2010 Bernard (21)	Rapid infusion of 2L ice cold lactated ringers post-arrest (VF only)	RCT Oct 2005 – Nov 2007	Victoria, Australia Intervention group - 118 Non-intervention group - 116	Hospital discharge home or to a rehabilitation facility (primary outcome): 47.5% intervention vs. 52.6% non-intervention (p=0.433). All other outcomes non-significant Early termination - futility	/
2012 Bernard (22)	Rapid infusion of up to 2L ice cold Hartmann's post-arrest (asystole or PEA only)	RCT October 2005 – November 2007	Victoria, Australia Intervention group - 82 Non-intervention group - 81	Hospital discharge home or to a rehabilitation facility (primary outcome): 12% intervention vs. 9% non-intervention (p=0.5). In those with cardiac aetiology subgroup, 17% intervention vs. 7% non-intervention (p=0.146) Early termination – logistics	/
2014 Kim (23)	Rapid infusion of 2L cold fluid 4^0C immediately post-arrest	RCT 15 Dec 2007 – 7 Dec 2012 (follow up until May 2013)	Seattle, Washington, US Intervention group – 688 (292 VF; 396 non-VF) Non-intervention group - 671 (291 VF; 380 non-VF)	Survival to hospital discharge (primary outcome): In VF 62.7% intervention vs. 64.3% non-intervention (p=0.69). In non-VF 19.2% intervention vs. 16.3% non-intervention (p=0.3) Neurological status of full recovery or mild impairment (secondary outcome): In VF 57.5% intervention vs. 61.9% non-intervention p=0.69. In non-VF 14.4% intervention vs. 13.4% non-intervention (p=0.3)	/
2011 Garrett (24)	Infusion of up to 2L cold saline intra-arrest (as soon as IV/IO access gained)	Before / after study Before: Oct 2008 – March 2009 After: April 2009 - Sep 2009 (pre-hospital TH protocol initiated in April 2009)	Large metropolitan area, US Before - 334 After - 208	Pre-hospital ROSC (primary outcome): 26.9% before vs. 36.5% after (p=0.018; AOR 1.83; 95% CI 1.19-2.81) (independent of fluid volume). In non-shockable subset 19.3% before vs. 29.9% after (OR 1.78; 95% CI 1.13-2.81). In shockable or witnessed shockable subsets, pre-hospital ROSC was higher in the after group, but not significantly. Survival to admission (secondary outcome): 28.4% before vs. 23.4% after (AOR 1.5; 95% CI 0.96-2.36) Survival to discharge: 12.5% before vs. 12% after (AOR 1.03; 95% CI 0.54-1.98)	+
2015 Schenfeld (25)	Rapid infusion of up to 2L (repeats of 500 mL bolus) cold saline as early as possible (intra/ post-arrest)	Before/after study: (introduction of a new protocol) Before: Nov 2007 – March 2009 After: April 2009 – Nov 2011 (pre-hospital TH protocol initiated in April 2009)	Existing QA database used as source – all patients treated in the therapeutic hypothermia clinical pathway of Carolinas Medical Centre (US) Before - 52 After - 80	Time to target temp following ROSC (primary outcome): No difference between groups Hospital survival, good neurological outcome (CPC 1 or 2) or survival at 1 year (secondary outcomes): No differences between groups	/
2016 Bernard (26) RINSE	Rapid infusion of up to 2L (30mls per kg) cold saline intra-arrest	Multicentre RCT Dec 2010 – Dec 2014	Melbourne, Adelaide and Perth, Australia Intervention group - 618 Non-intervention group - 580	Survival to discharge (primary outcome): 10.2% intervention vs. 11.4% non-intervention (p=0.51). No differences between groups when stratified by shockable status ROSC (secondary outcome): In shockable subgroup, 41.2% intervention vs. 50.6% non-intervention (p=0.03)	/

Type of association: + intervention confers benefit; / intervention does not confer benefit

SUPPLEMENTAL MATERIAL (PART B – NON-PHARMACEUTICAL STRATEGIES) – Data supplement published online

Supplemental Table 1: Additional information for each identified study

Year and lead author	Limitations	Additional results	Other
Use of a modified resuscitation protocol			
2008 Bobrow (1)	• Not an RCT • Unable to standardise post resus care • Cannot exclude Hawthorne effect • AHA guidelines were updated during this time period so some fire departments were using 2000 guidelines and some were using 2005 • Outcome data unknown for 2 patients in ITT analysis and 7 in PCA • Neuro outcomes unknown for 35% survivors • Cannot exclude ascertainment biases in PCA – perhaps enthusiastic paramedics provided MICR and less enthusiastic did not • Paramedics may have also provided MICR to the pts who were more likely to survive	Protocol compliance analysis: 61% of cardiac arrests treated after training, met the 4 MICR compliance criteria Survival to hospital discharge: 3.8% controls v 9.1% cases adjusted OR 2.7 CI 1.9-4.1 ROSC: 17.3% before v 28% after OR 1.9 CI 1.5-2.3 Survival to admission: 15.1% before v 21.9% after OR 1.5 CI 1.2-2.0 Survival with witnessed VF 11.9% before v 28.4% after OR 3.4 CI 2.0-5.8 Neuro data only available for 84/129 survivors (65.1%). 81.6% before v 80% after	Included: All OHCA pts on who resus was started. Excluded: obvious death and DNR (resus not started), <18 years, witnessed by EMS, trauma, drowning or non-cardiac causes. Protocol: Initial 200 compressions, rhythm analysis and shock, 200 compressions. ETT delayed and adrenaline given asap, passive O2 insufflation (however due to dramatic change BVM was permitted at 8/min). More pts intubated after MICR p<0.001, other characteristics no diffs. ITT analysis (before/after) as well as protocol compliance analysis (who was actually treated with MICR versus who wasn't). PCA: in cases there were more men, ETT more frequent and younger. Same otherwise. 60 additional fire departments for PCA controls.
2008 Kellum (2)	• Validity and effect of exclusion criteria – all shockable patients reviewed to see if exclusion	N/A	Included: Adult witnessed cardiac aetiology shockable OHCA.

	criteria would prejudice results – no evidence found of prejudice • Data reviewed by author not blinded to outcome – every effort made to be impartial and apply criteria to decisions. CPC scores are well defined • Did not assess adequacy of bystander CPR efforts • Did not assess quality of CPR or CCR • Adherence to protocols was not investigated • Hospital ICU protocols were not specifically addressed or altered • Did not quantitate or study AED deployment • Ability to interview rescuers of cases but not controls – would only have affected ‘witnessed’ status • Did not study inappropriate shocks / but if defib downloads available they were compared with records to check for ‘shockable’ status • Metronome usage sporadic in cases and not at all in controls • Hawthorne effect not addressed – other than extending the project to 3 years (as opposed to 1 as per earlier study) • Unknown survival advantage of each intervention as many introduced simultaneously • Do not know how effective the protocol would be on patients who had EMS interventions initiated >10mins • Do not know effect on not witnessed or non-shockable events		Excluded: Resus not initiated or terminated in the field, DNR, non-cardiac aetiology, witnessed by EMS, <16 years. Protocol: 200 compressions before rhythm analysis. Single shocks not stacked shocks. Post-shock pulse and rhythm check eliminated- continuous compressions immediately post shock. Teaching emphasis on compression quality – 100 per min, metronome use, full chest recoil. If only 1 responder on scene AED pads attached before chest compressions. Airway management delayed. If the arrest was witnessed and <12mins breaths not performed until ROSC or after 3 cycles. CPC score 1 deemed normal. 3tiered system – first responders with AEDs (law officers or EMS).

2009 Garza (3)	• CPC only recorded for cases (not available before protocol change) • Retrospective – vulnerable to bias • Impossible to point to 1 change within the protocol that would result in such a dramatic rise in survival • Hospitals and post resus care not studied although no hospitals were doing TH • Possible Hawthorne effect - post protocol may have received better quality CPR • Impossible to determine how closely paramedics and firefighters chose to follow the protocol – no electronic data from defib to show rate / quality of chest compressions or no flow periods • Resultant reduction in ventilations	Of the 25 cases that survived, 88% discharged with a CPC score of 1 or 2 Log regression analysis of patient survival of overall group: exposure to new protocol sig improved survival OR 2.17 1.26-3.73 Median response time interval was less for survivors than non-survivors in cases and controls but not sig	Included: Adults, cardiac aetiology. Subgroup of bystander witnessed pts presenting shockable rhythm only. No differences between baseline characteristics in witnessed subgroup. Revised protocol meant to improve chances of survival according to the 3-phase model of survival. If no good bystander CPR underway, 200 compressions at 50:2. Undertaken as part of KCMO EMS system quality improvement programme 2005.
2015 Nichol (4)	• Some minor differences between groups not considered clinically significant • Small intended differences in CPR process (part of strategy) • A lot of patients excluded from the per-protocol analysis as the automated algorithm could not classify to case or control – (more controls were excluded than cases and there were imbalances in characteristics and treatments between these groups) • The difference in chest compression fraction between groups was small which is likely to be the Hawthorne effect – Outside of a trial this difference is likely to be larger	Hospital free survival sig shorter in the intervention group p=0.004 Compliance only (referred to as per-protocol population within study - determined by application of an automated algorithm to the CPR process data) – Survival lower in intervention group p<0.001 (adjustments for pre-treatment confounders attenuated the difference)	Included: Adults, non-trauma OHCA that received chest compressions by providers of the participating EMS agencies. Excluded: EMS witnessed, AHD, traumatic injury, asphyxia cause, uncontrolled bleeding, known pregnancy, pre-existing tracheostomy, prisoners, initial CPR by non-participating EMS provider, mechanical chest compressions before manual, advanced airway before ROC EMS agency arrival, priori not to participate. Run in phase and adherence demonstrated before inclusion.

	• Imbalance of patients randomised to cases and controls due to uneven number of cluster periods, variation in time of first cluster period (before cross over) between agencies and suspension of some agencies by the study committee • Between group differences in characteristics and treatments received • Post resus care not mandated • Oxygenation and ventilation not measured • Other interventions not reported		
2013 Bobrow (5)	• 1 patient missing outcome data • 3 patients missing functional outcome scores • ++ patients missing CPR quality data • Non-randomised – Unknown confounders or the Hawthorne effect may have led to the improved outcomes, although when analysed there was no evidence of secular trend in phase 1 and no evidence of Hawthorne effect • 1 EMS agency • 1 CPR quality measurement • 1 monitor / feedback device • Unable to determine the relative influence of each intervention	All CPR metrics showed a significant improvement from phase 1 to phase 2 for both imputed and non-imputed data	Included: Age ≥18 and OHCA of presumed cardiac aetiology with a resuscitation attempts by EMS. Excluded: Resuscitation not initiated, DNR, arrest witnessed by EMS or a presumed non-cardiac cause. Adjustments in calculations made for witnessed arrest, initial rhythm, TH, age and MICR protocol compliance. MICR protocol compliance measured by several CPR quality components, as recorded by the monitor.
2016 Hopkins (6)	• Study design may have been affected by temporal trends in OHCA survival • Multiple interventions undertaken at once so unclear which individually or combination is/are the contributor/s – individual impact cannot be established • Difficult to ascertain which components are generalizable	Number needed to treat to gain an additional neuro intact survivor =12 Non-sig difference in proportion of cases in which resus was attempted 36% v 39% respectively p=0.24	Included: All OHCA patients with an initiation of CPR. Excluded if no CPR or arrest due to trauma, drowning or strangulation. Changes in CPR depth, rate and CCF over time were analysed.

	• Unadjusted results only reported • Improvements may have been due to in-hospital care (would not account for increased ROSC) – This would highlight importance of transport to appropriate facility	CPR rate decreased and depth increased over time p=0.006 but CCF did not significantly change p=0.8	Pt demographics and resus variables were similar with the exception of bystander CPR and ROSC in the field which were both higher. Field pronouncement higher in the post phase 41% v 25% p<0.0001. Post arrest angiography in initially shockable pts higher in the post phase, as per strategy, although rates of in-hospital TTM were similar in both periods. Various CPR quality improvement initiatives - Real time CPR feedback technology, post-incident feedback on all cases, rhythm filtering technology, on scene resuscitation encouraged, passive O2 for first 6-8mins in adult witnessed arrest of cardiac aetiology, ITD added to advanced airway in July 2013), simplified medication algorithm (removal of atropine, amiodarone to replace lignocaine, IO first line access and cooling commenced on ROSC), EMS crew team training (pit crew approach) and more appropriate transport destinations.
2016 Pearson (7)	• TFCPR group consists of less comorbid conditions including cancer, diabetes, coronary artery disease, hypertension and respiratory illness, than the standard CPR group • TFCPR (v standard CPR) group had similar shockable initial rhythm, fewer witnessed arrest (sig), fewer ETT (as per protocol) (sig), higher bystander CPR rates (sig), more arrests after EMS arrival (sig) and higher CPR feedback device utilisation (as per protocol) (sig).	Logistic regression with controlling for multiple characteristics: TFCPR associated with increased good neuro outcome OR 1.5 CI 1.2-1.8 Witnessed arrest, initial shockable rhythm and in-hosp	Included: Adult non-traumatic arrests of presumed cardiac aetiology where resus took place (EMS performed CPR or defibrillation). Excluded: Age less than 18, missing data on whether TFCPR was used and missing hospital outcome data. Pre-intervention was standard CPR with ACLS 2010 protocols (30:2 prior to advanced airway placement).

	• Observational analysis • Self-reporting of agencies for if they performed TFCPR and implementation date • Unknown consistency between agencies • Unrecognised bias from non-randomised design • Unrecognised pt management and outcome factors • CPR factors and quality not measured • Did not adjust for other factors such as response times, location of arrest or in-hosp care • EMS agencies self-reported implementation dates. •	TH also associated with good neuro outcome Elements negatively associated were mechanical CPR device use, CPR feedback device use and ETT NNT with TFCPR to result in 1 additional good neuro outcome = 29	
Use of a mechanical chest compression device			
2012 Jennings (8)	• Low number of cases - Too few cases involved survival to hospital discharge to consider this a legitimate outcome • Not randomised	Higher survival to admission but lower survival to discharge (no statistically significant) Overall - cases 70% more likely to survive to hospital but not significant Bystander witnessed, cardiac aetiology subgroup - cases 80% more likely to survive to hospital but not significant	Included: All adults (≥18 years) where LDB used. Cases matched by known predictors of survival (age, gender, response time, presenting rhythm and presence of bystander CPR) to select controls - selected from 1610 cardiac arrest which occurred during the study period. 3 populations settings – Geelong, Shepparton and Mildura. Devices used by ALS and MICA paramedics – on front line vehicles.
2014 Wik CIRC (9)	• Survival to hospital discharge not available for 12 pts • MRS only available for 310/429 pts who survived to hospital discharge (70% and 74%) –	Survival to hospital discharge AOR (when adjusted for covariates and interim analysis): 1.06 0.83-1.37	Included: >18 and OHCA of presumed cardiac aetiology. Excluded: Pregnant, DNR in place, too big for device, prisoner or ward of state, received mechanical chest

	discharged before consent could be obtained. Missing in 28% overall • No blinding • Could not standardise post resus care • Post enrolment exclusions • No longer term outcomes than survival to hospital discharge • Compression depth was not measured.	CCF mean: intervention 74.7% v manual CPR 79.0% Unpublished results: Confirm the link between high quality CPR and survival from CA. Mechanical chest compression devices overcome the difficulties in inconsistent performance of manual CPR	compressions prior to randomisation or if unit with device had response time more than 16 mins. Variety of site types in order to enhance external validity 3 phases: 1) in field phase– experience in using the AP, 2) run in phase- pts were randomised and data assessed for protocol compliance and to test the Hawthorne effect, 3) inclusion phase- all data used in statistical analysis. Sites not in phase 3 until they met protocol compliance criteria. Randomised by sealed envelopes. Modified ITT analysis which excluded those retrospectively found to meet exclusion criteria. Most demographic characteristics similar apart from higher occurrence of VF/VT in controls p=0.02. Focus on ensuring high quality chest compressions. 4-hour training programme and continuous monitoring and reporting of compliance.
2011 Smekal (10)	• Some manual compressions before LUCAS (while deploying etc) • Compressions ongoing through defibrillation • Manual CPR quality not measured • Different algorithm between cases and controls	N/A	Excluded: Pregnant, <18 or trauma. Cases got 2 cycles of a specialised algorithm: If shockable 2.5 min cycles with shock during compressions at 90 secs; if non-shockable 1.5 min cycles. After 2 cycles revert to ERC guidelines but with LUCAS. Cases treated with ERC 2000 guidelines.

			True randomisation by opening a sealed letter at the patient's side. No diffs in demographics. ITT analysis. LINC pilot.
2013 Axelsson (11)	• Change in guidelines in 2005 between period 1 and 2 (although analysis done on period 2 only) • In period 2 only 60% of cases were treated with LUCAS • Period 2 only: No diff in location of arrest, aetiology or VF as initial rhythm but there were fewer women and fewer crew witnessed cases in the LUCAS group. More pts had a bystander witnessed event and bystander CPR in the LUCAS group. The number of pts treated with adrenaline was higher in the LUCAS group and the delay to defibrillation was 6 mins longer. • Pts who were rapidly defibrillated to a pulse generating rhythm did not get LUCAS • Most survivors in period 2 appear to have received ROSC early so did not require LUCAS or adrenaline • LUCAS targets a high-risk group with a low chance of survival so requires a large sample to reach a power of 80%	Multivariate analysis showed independent predictors of survival to be VF/VT as initial rhythm and crew witnessed events. If treated with LUCAS OR 0.5 (95%CI: 0.28-0.92) or adrenaline OR 0.14 (95%CI: 0.08-0.26) - survival reduced Increase in survival from period 1 to 2	Inclusion criteria was all OHCA patients where CPR was attempted.
2014 Rubertsson	• Differences between cases and controls were number of defibrillations delivered by EMS on	No survival advantage	Included: 18years+ in whom resus was considered appropriate.

LINC ([12](#))	scene and time to first defibrillation (1.5mins longer in cases) – may have been results of algorithm. Unknown how much the 2 different algorithms have influenced the results • LUCAS with compressions ongoing through defibrillation • Adherence to algorithm/ manual CPR quality was not evaluated but is reflected in the number of defibrillations delivered (it is probable responders did not adhere to the mechanical CPR algorithm in at least 24% cases as no shocks were delivered) • Impedance data collected in 10% of patients was recorded and showed a chest compression fraction of 0.78 in controls and 0.84 in cases • Due to the sample size this study could not rule out a 3.2% benefit or similar sized harm from mechanical CPR relative to standard CPR		Excluded: traumatic arrest, known pregnancy, a body size too large or small to fit machine, pts undergoing defibrillation before machine arrival, crew witnessed arrests that achieved ROSC after immediate defibrillation. True randomisation by opening a sealed letter at the patient's side. Cases were run in 3-minute cycles of continuous compressions and shocks delivered at the 90 sec mark if required (initial countershock delivered regardless of rhythm). Controls treated in 2 min cycles as per ERC guidelines. Post resus care included mild hypo at 32deg and PCI if indicated – no significant differences between groups Missing values were imputed as worst outcome - p<0.48 ITT analysis 4-hour survival used to minimise effect of post resus interventions
2015 Perkins PARAMEDIC ([13](#))	• Cross over of staff from trial vehicles to non-trial vehicles so a higher quality of CPR likely to have been provided to controls as well as cases • 60% of patients randomly assigned to LUCAS actually received treatment with the device – This was accounted for in the various analysis methods ie. ITT (reflects implementation into	Survival at 3 months very similar to survival at 30 days – suggests little mortality between 30 days and 3 months	Included: If a trial vehicle was the first ambulance service vehicle on scene, resus attempt, 18 years+. Excluded: Traumatic aetiology and apparent pregnancy Cluster were ambulance service vehicles (rather than individual patient randomisation), assigned with a

	routine practice as takes into consideration all the real life problems) and CACE (reflects treatment effect of LUCAS where compliant with trial protocol and device was actually used • Sample size reassessed and increased part way through (based on LUCAS use, outcomes at that stage unknown) • Selection bias reduced by study design due to including all cardiac arrests where a trial vehicle was first on scene. However, paramedics still had to decide to make a resuscitation attempt which may have been precipitated by the presence of a LUCAS device – no evidence of resuscitation thresholds found	No difference between groups in sub group analyses of witnessed status, type of vehicle, bystander CPR status, aetiology and region Subgroup analysis by shockable status of initial rhythm showed lower 30-day survival in cases (OR 0.71 95%CI: 0.52-0.98) – Not a priori of the study so should hypothesis generating only (perhaps related to interruptions in CPR, delay in shock or more adrenaline received)	computer-generated randomisation sequence (stratified by station and vehicle type) – Ambulance dispatchers unaware of the allocations ITT analysis – complier average causal effect (CACE) analyses used Selection bias minimised Ratio of approx. 1 LUCAS vehicle to 2 control vehicles due to limited number of LUCAS devices available (143) LUCAS 2 rather than LUCAS 1 as per other trials Specific training protocol with LUCAS followed Both groups received ratio 30:2 before intubation and continuous compressions post intubation No major imbalances in characteristics between groups Meta-analysis with 2 previous trials conducted – Showed no evidence of superiority in outcomes. Pragmatic approach to training etc – Reflects most likely true experience and highlights potential limitations of translation from efficacy trials to real life practice

2015 Zeiner (14)	• Low number of cases meant a separation into 3 subgroups (to distinguish between Autopulse and LUCAS) would not yield significance • Group receiving manual compressions were older 70+- 10 years v 63+- 9 years (p≤0.001) with a smaller proportion of males than the mechanical CPR group (59.5% v72.4% p<0.001) • Mechanical CPR group had a higher rate of shockable patients 33.7% v 22.1% p<0.001, more witnessed arrests 55.8% v 54% p=0.614 and more bystander CPR 54.1% v44.7% p=0.008 – therefore more favourable initial position for a good outcome • Duration of CPR longer in the mechanical group (p<0.001) – May explain worse outcomes • No reported protocol / guideline for mechanical chest compression device use, so un-measureable selection bias likely • More LUCAS than AP used 239 v 44 explained by the procedures of the Vienna Ambulance Service • Single urban area • No standardised post arrest care	In survival analysis mechanical CPR had a significant direct association with in-hospital mortality when adjusted for age, gender, aetiology, initially shockable, witnessed status, bystander BLS, hands on fraction and larynx tube application – Hazard ration per 1-SD 1.59 CI 1.21 – 2.09 p=0.01 No differences between quality of CPR provided by mechanical v manual	Included: If suffering an OHCA and receiving resuscitative efforts by EMTs or physicians of the enrolling ambulance service. Cases included those where the device was actually used v controls where it was not. Where it was bought to scene or prepared and not used were controls. 16 emergency physician manned vehicles – 8 equipped with Autopulse and 8 with LUCAS. Additionally, field-supervisor staffed vehicles are equipped with LUCAS. Data collect via patient EMS records, defibrillator data, hospital records and discharge letters and contacting the affiliated physician at the admitting department.
Intra-thoracic pressure regulation			
2008 Aufderheide (15)	• Conflicts of interest – affiliations with Advanced Circulatory Systems who make the devices • Swine study undertaken as part of this study • Some cases received TH • Historical controls and neuro outcome data not available for most sites at this time	N/A	Part of study fits inclusion / exclusion criteria - Human component only presented.

	• Beneficial effects cannot solely be attributed to ITD but only on a combination of interventions • Inconsistencies across sites – some sites showed a higher number of non-VF/VT surviving to hospital discharge but the largest site did not		
2011a Aufderheide ROC Primed (16)	• Early termination in Nov 2009 – termination recommended because interim analysis showed that findings would not change with continuation • Haemodynamics, intrathoracic pressure, chest recoil, ventilation rate and duration or the effects of ITD use during gasping and spontaneous vent, were not directly measured • CPR process measures were not recorded in all cases • Modified Rankin Score lacks validation for CA • ITD placed within 5 mins in only 61.5% of pts • 2 components to this trial, the other being early versus delayed rhythm analysis – most patients were enrolled in both which may have complicated the intervention	Post hoc analyses of sub groups showed that when defined by CPR fraction, pts in the 2nd lowest quartile (59.9-71%), cases had a sig increase in survival to discharge with satisfactory functional status (p=0.006)	All adults with non-traumatic arrest with resus by EMS who were participating in ROC. Excluded if incarcerated, pregnant, DNR, exsanguinations, severe burns, tracheostomy or use of mechanical CPR device. Responders encouraged to implement within 5 mins of arrival – to BVM or advanced airway. EMS personnel were required to provide evidence of acceptable performance to an internal monitoring committee before permitted to participate. CPR performance and compliance monitored. Baseline characteristics no different.
2011b Aufderheide ResQtrial (17)	• Midpoint analysis suggested an increase in sample size from 700 per group to 1348 per group to maintain original study design - Initially a third arm was planned-ITD only (to ascertain relative contribution of ITD alone) with half the proportional enrolment planned than the other 2 arms. Enrolment was slower than expected and due to funding issues, the group was discontinued early and not included in analysis • Study was stopped due to funding issues in 2009 at 1653 pts (original criteria were still applied –	No significant differences between rhythms Disability scores did not differ between groups No difference in adverse event rate overall but more people had pulmonary oedema in ACD+ITD group	Included: ≥18 years presumed cardiac aetiology Excluded: less than 1 min CPR by EMS, AAM unsuccessful, intubation with a leaky or uncuffed device, stoma, tracheotomy or tracheostomy, non-cardiac aetiology. Medical service personnel underwent hands on training before the study and every 6 months during. Computer generated block randomisation by an independent statistician.

	80% power P<0.05) This could have changed the primary findings • Improved perfusion OH might result in more cases being provided cardiac catheterisation • EMS providers not blinded • Could not establish relative contribution of ITD, ACDCPR, timing lights, metronome • Some survivors refused to consent for further participation or release of data • Many conflicts of interest – affiliations with Advanced Circulatory Systems who make the devices	11% vs 7% in SCPR (p=0.015)	
Application of therapeutic hypothermia			
2010 Bernard (18)	• Only half of the cases received the full amount of cold fluid due to short transport times. Therefore, smaller decrease in mean temp and smaller difference between groups than expected • 75/118 (48%) received 2000mls, 11/118 (9%) received 1500-2000mls, 37/118 (31%) received 1000-1500mls, 5 received 500-1000mls (4%) and 8 (7%) received no ice-cold fluid • Not possible to blind paramedics and hospital staff to treatment (although treatment followed standard guidelines) • Tympanic temp measurement may be inferior to other methods • Study terminated early… It is possible that with larger number a trend may have been visible • 164/398 (41%) potentially eligible patients were not enrolled, unknown reason – identified by VACAR Victorian ambulance CA register	Study stopped at interim analysis of 200 participants due to futility EMS temp on hospital arrival lower in intervention group in ED and 30mins post ED arrival – see table 2 for p values	Included: Adult VF OHCA, ROSC with sys BP>90, cardiac arrest>10mins, age15+, IV access available. Cardiac aetiology only. Excluded: Not intubated, dependent upon others for activities of daily living before cardiac arrest, already hypothermic, obviously pregnant. Temp measured with a tympanic probe pre-hospital and bladder probe in hosp. Randomisation by ICPs on scene and envelopes. Patients also received 0.1mg/kg midazolam and 12mg pancuronium to suppress shivering. Frusemide indicated if PO developed. On hospital arrival a further 10-20mls /kg ice cold lactated ringer administered in cases.

	• No long-term outcomes assessed – possible that subtle improvements may have been seen – beyond scope • No assessment of intra-arrest cooling • No assessment of other rhythms		Controls received standard pre-hospital therapy – IV midazolam/ pancuronium only if required for ventilation. On hospital arrival 40ml/kg ice cold lactated ringers administered to induce hypothermia. In hospital target temp 33 for 24 hours for all. All other aspects of care at physicians' discretion Cases and controls similar in characteristics.
2012 Bernard (19)	• 146 patients eligible but not enrolled. Not possible to determine reasons • Significant proportion had a non-cardiac cause – 43% cases and 46% controls – many of these would have died from the underlying cause of arrest not just from neuro aspect and therefore would not benefit from TH (future studies should look at cardiac cause only) • Not all cases received the correct amount of fluid – 36/82 (44%) received 2000mls, 5 (6%) received 1500-2000mls, 21 (26%) received 1000-1500, 7 (9%) received 500-1000mls and 13 (16%) received no cold fluid – largely due to short transport times (findings may not be applicable to services with longer transport times) • Of those who survived 36 hours, 93% cases v 79% controls achieved TH (temp<34) at some stage – may be due to lack of appropriate cooling technology in hospital – may explain no diff in outcomes • Future studies should look at cooling intra-arrest as this one did not assess that • Treatment allocation was blinded but actual treatment provided was not able to be	Cases: Median of 1500mls ice cold fluid. Mean decrease in core temp: Cases 1.4deg v controls 0.2deg ($p<0.001$). Time to <34deg: Cases 3.2hours v controls 4.8hours ($p=0.0328$). Of all those admitted to ICU, sig diffs between temps of groups only in 1st hour (from 1st temp taken in ED) – may explain no diffs in outcome	Asystole or PEA only. Otherwise methods same as Reference 24, apart from all aetiologies in this study and fluid type. ITT analysis. Stopped due to futility of VF trial (24) and logistic difficulty to carry on with this concurrent trial therefore an effect may have been missed.

	• Tympanic temp used – slightly less accurate than other methods • Longer follow up not measured		
2014 Kim (20)	• All aetiologies other than trauma included – may be better if just cardiac aetiology • 1013 pts that met inclusion/exclusion criteria were not enrolled – various reasons eg. Missed, deemed as too unstable and others • Various hospital treatment possible but well controlled for and all cooled for up to 24 hours – not controlled by study – no sig diffs between early angiography (within 6 hours of arrival) or reduction in level or withdrawal of life support in cases and controls • Not possible to blind paramedics • Ideally controls should have received 2l normal temp fluid (to strictly relate outcomes to temp), pancuronium and diazepam. • 1364 pts enrolled but 5 were withdrawn due to being incarcerated at time of enrolment! Therefore 1359 included for primary analysis. • 12/292 (4%) of VF cases and 27/396 (7%) of non-VF cases did not receive any fluid (rearrest, death or lack of time to hospital) • More rearrest in cases may increase risk of death later in hospital • Low oxygenation and blood gas pH are predictors of poor outcomes (as observed in cases). • Current study could not detect longer term outcomes past discharge – outcomes can improve for at least 6 months post discharge	Decreased core temp by 1.2deg CI -1.33- -1.07 in VF and by 1.3deg CI -1.4- -1.2 in non-VF by hospital arrival. In VF time reduced by just over 1 hour (4.2hours v 5.5 hours sig) to reach temp <34deg compared to controls (measured only in those who achieved temp <34). Similar in those without VF Median length of stay similar in both groups for VF and no VF Significantly more rearrest in field in cases: 26% v 21% p=0.008, and pulmonary oedema on 1st chest x-ray, use of diuretics and longer on scene time Cases had significantly lower oxygenation on ED arrival (SpO2 and PaO2 from blood gas) and first arterial blood gas pH	Included: Adult, non-traumatic arrest (but all other aetiologies included), ROSC, tracheal intubation, IV access, successful placement of oesophageal temp probe and unconscious. Excluded: DNR, unable to intubate. Oesophageal temp used. Saline given as soon as paramedics had resuscitated the patient. Adults 18 years+, non-traumatic OHCA ROSC, had an oesophageal temp ≥34, were intubated, had IV access and were unresponsive. Randomised by phone call to physician at hospital who opened an envelope. Cases also given 7-10mg pancuronium and 1-2mg diazepam (not given to controls). If pts had another cardiac arrest, saline stopped and standard protocols followed. Randomisation stratified by first recorded rhythm (VF or non-VF) and destination hosp. Baseline characteristics not different including temps.

			Fluid stored in fridges on ambulances at 4°C
2011 Garrett (21)	• Accuracy of fluid volume questionable – as per patient care report which is often rounded to easily reported number • Unsure how much of the fluid was received prior to ROSC – possible that a sig proportion of fluid given post ROSC • Protocol change may have triggered improvement in treatment overall eg. CPR quality – chest compression quality not measured • Pre-hospital temps not recorded – assumed cold fluid would cause a predictable decrease in body temp dependent upon quantity • Do not know amount of fluid given in controls. May be different although should have been normal bolus as part of resuscitation • Average amount of fluid given to cases was 548mls	250-500mls of saline ROSC OR 1.83 (sig) compared to no fluid. >700mls fluid ROSC OR 2.4 (CI 1.41-4.24) (Reported in discussion only). Linear association between amount of cold saline and pre-hospital ROSC – Significant changes at 2 point along the curve: 200mls (when compared with patients who received less than 50mls chilled saline) and; 700mls (when compared with those who received 200mls)	Included: Non-traumatic arrest 18 years+. Excluded if pregnant, arrest secondary to drowning or resus not attempted ie. DNR or rigour etc. Fluid cooled in fridge to ensure consistent temps. Suggestions of smaller amounts of fluid not changing overall body temp but changing intra cardiac temp and subsequent effects on endocardium and myocardium. This may prime the myocardium increasing likelihood of ROSC.
2015 Schenfeld (22)	• Main objective is to determine if cold fluid improved time to target temp (not a patient outcome) • Patients in the pre-hospital cooling group were more likely to have received bystander CPR and field AED use - Pre-hospital 'focused CPR' protocol initiation several months before TH protocol, likely to be the cause • Lack of difference in outcomes may have been due to insufficient power to detect changes	When groups divided by fluid initiation time (intra-arrest or post ROSC) – no differences between groups in outcomes Significantly longer pre-hospital time intervals in those receiving PH cooling 57/80 cases had cooling initiated pre-ROSC	Included (PH cooling): Cardiac aetiology, all rhythms. Strategy implemented in both intra-arrest and post ROSC phase and patients with the goal of earliest possible initiation of cooling. Included (IH cooling - ground pre-hospital transport arrival only): Resuscitated non-traumatic cause with persistent GCS≤8 for at least 15mins post ROSC (extra level of consideration for non-shockable cases – discussion between emergency physician and critical care physician). Excluded: DNR, severe terminal illness, pregnancy, encephalopathy, active haemorrhage, severe systemic

	• Non-randomised design so unrecognised bias a possibility • Inclusion of non-shockable rhythms at the discretion of physician • Unrecognised confounders to patient management or outcome • Not necessarily generalisable to regions with longer transport time • Other cooling methods not investigated • Unknown how many patients had their cooling discontinued due to shivering • First temp taken at hospital		infection, arrest duration>60mins – clinical discretion superseded the relative contraindications All patients admitted to the ICU with the intention to undergo TH were included regardless as to the current extent of TH, although only those with TH initiated PH were included. Infusions given as 500ml rapid IV bolus. Repeat rounds where required up to 2l – discontinue if shivering develops. Ambulances with fridges maintaining fluid at 4deg. In hospital cooling included ice packs to groin, axilla and neck and continuation of cold IV fluid up to 30mls/kg and CR band arctic sun cooling device with a target temp of 33deg.
2016 Bernard RINSE (23)	• Sample size planned to be 2512 – study finished early due to a change in hospital cooling target temperature from 33 to 36 based on the target temperature trial – If trial had continued it would have been unlikely to show a diff in hospital outcomes • Staff were not blinded • Hospital intervention data not collected • Tympanic temp may not reflect core temp • Only collected data from approx. 10% of all cardiac arrest patients – not feasible to collect data on why not enrolled • Other techniques should be considered such as intra nasal cooling and surface cooling	Adjustments for fluid volume did not alter results	Included: 18 years+ who had resus commenced, were in cardiac arrest on EMS arrival, had IV access established and were still in cardiac arrest after initial resus treatments. Excluded: Aetiology of trauma inc hanging, suspected of intracranial bleed, pregnancy, already hypothermic (<34deg), inpatients at a hospital or an AHD in place. Randomisation by opening an envelope containing a computer generated random treatment allocation. Paramedics carried 2l normal saline in a cold insulated container that maintained the temp at approx. 3 degrees using an ice block changed every 12 hours.

			Treatment ceased if tympanic temp reached 33 degrees or if pulmonary oedema suspected. Study analysis followed ITT methodology. No differences in characteristics between groups. Cases had significantly longer duration of CPR and more adrenaline. More pulmonary oedema seen at hospital in cases.

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2.3 Chapter Summary

- There has been a recent increase in the volume of research undertaken to improve outcomes from OHCA. These findings required consolidation.
- The aim was to conduct a systematic search and review to identify strategies which may be used by paramedics in Australia to improve outcomes from OHCA. Additionally, to describe and synthesise the evidence to make recommendations for improved outcomes in high income countries with developed health care services.
- In February 2017 four databases were searched systematically for papers published between 2007-2017 describing strategies appropriate for use when resuscitating adult patients in OHCA from presumed cardiac aetiology.
- The search identified 28 separate studies for final review, incorporating six strategies. These were: use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation; vasopressin administration; thrombolysis administration; and application of therapeutic hypothermia.
- Extensive evidence tables summarise the findings for each study within each of the six strategy groups.
- Part A presents the two pharmaceutical strategies - vasopressin administration and thrombolysis administration. The findings do not support the introduction of the administration of either vasopressin or thrombolysis.
- Part B presents the four non-pharmaceutical strategies - use of a modified resuscitation protocol; use of a mechanical chest compression device; intra-thoracic pressure regulation; and application of therapeutic hypothermia. Forest plots provide a visual summary of results (survival to hospital discharge or survival to 30 days) for the non-pharmaceutical strategies. The only strategy group which showed adequate evidence to warrant immediate implementation recommendations was use of a modified resuscitation protocol to improve the quality of CPR (preferably with some degree of pit crew approach).
- Further research with more rigorous designs is required for pharmaceutical and non-pharmaceutical strategies, coupled with continued monitoring of the evidence base.

- Overall, the systematic search and review demonstrated that there is a shortage of high-quality evidence for strategies which may be used by paramedics to improve outcomes from OHCA.

2.4 Final Word (Chapter 2)

This Chapter represents a broad review which identifies, describes and consolidates the findings of studies investigating strategies that may be used by paramedics to improve outcomes from adult OHCA of cardiac aetiology. This informs recommendations for future strategy development and further research so is an important addition to the literature. Only one strategy warranted a recommendation for immediate implementation. Overall, there is little high-quality evidence to inform recommendations for strategy implementation. This finding is complemented by the subsequent Chapters of this thesis (Chapters 4-6; Publications 3-5). Collectively, these Chapters explore outcomes from OHCA by demographic factors such as gender, age geographical remoteness and socio-economic status, and are intended to identify target populations to assist with strategy focus and development.

Chapter 3: Methods

Table 1: Abbreviations

A full list of abbreviations can be found at the beginning of the thesis. However, as there are many abbreviations used throughout this Chapter specifically, the relevant abbreviations are replicated here.

ARIA	Accessibility/Remoteness Index of Australia
DOB	Date of birth
DLU	Data Linkage Unit (located in the Health Statistics Branch within Queensland Health)
eARF	electronic Ambulance Report Form
ISREU	Information Support, Research and Evaluation Unit, Queensland Ambulance Service
OHCA	Out-of-hospital cardiac arrest
OHCA Registry	Out-of-Hospital Cardiac Arrest Registry
QHAPDC	Queensland Hospitals Admitted Patient Data Collection
RG Death Registry	Registrar General Death Registry
SEIFA	Socio-Economic Indexes for Areas (SEIFA)

3.1 Overview

The systematic search and review described in Chapter 2 identified a lack of high-quality research to identify strategies to improve outcomes from OHCA in the pre-hospital environment. One of the main recommendations of the review was that large epidemiological studies should be undertaken to inform target populations for strategy development. The following three Chapters (Chapters 4-6) are informed by this recommendation.

Chapter 3 provides an overview of the main methods used for the remainder of the thesis, in which aims 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia)* and 3 *(To investigate predictors of survival from OHCA)* are addressed. In this Chapter are ethics, data access, sources and linkage, and detailed description of the main variables studied in the thesis (specifically, geographical remoteness, socio-economic status, and the various outcomes from OHCA).

3.2 Research Ethics and Access

Ethical approval for this study was obtained from Prince Charles Hospital Human Research Ethics Committee (approval number 15/QPCH/265), and from James Cook University Human Research Ethics Committee (approval number H5752). Access to confidential data was obtained via the Public Health Act through Queensland Health (approval number RD006708). Copies of the ethics and Public Health Act approvals are shown in Appendix G.

3.3 Data Sources

This study involved the linking and merging of OHCA cases from three independent data sources, as follows:

1) QAS Out-of-Hospital Cardiac Arrest (OHCA) Registry – Captures all cases of OHCA attended by QAS paramedics;

2) Queensland Hospital Admitted Patient Data Collection (QHAPDC) – Captures all cases in which a patient is separated from public and licensed private hospitals in Queensland, excluding patients who visit only the Emergency Department);

3) Queensland Registrar General (RG) Death Registry – Captures all deaths in Queensland

See Appendix H for further information on the data sources and variables provided.

3.4 Data Linkage

Data linkage is a method used to create links between records within different data sources that are thought to relate to the same person. This allows the collation of a broader, more detailed dataset, so investigations can also be broader and more specific to the research question. Additionally, data linkage allows a more accurate and complete collection.

Different datasets being linked often contain the same variable e.g., age or gender. If entries are contradictory between datasets, the one deemed likely to be the most accurate can be used. Similarly, if the entry in one dataset is missing, the information can be drawn from the other. Therefore, data linkage reduces the impact of some of the common limitations of using large administrative data collections and brings greater rigour to any study methodology.

There are also limitations to linking data. Although linkage software is well developed and rigorously designed with sophisticated quality assurance processes, there is a risk of false positives (incorrect links) and false negatives (failed links). However, this is likely to be infrequent.

The initial sample for this thesis was taken from the QAS OHCA Registry. Inclusion criteria were all patients in Queensland aged 18 years or over, who experienced a confirmed cardiac arrest of presumed cardiac aetiology and were attended by QAS Paramedics during a 13-year period (2002–2014). Cardiac aetiology is presumed in male persons ≥40 years old or in female persons ≥50 years old, when there is no evidence to suggest that another classification is more appropriate. This may be confirmed by the presence of cardiac related symptoms such as chest pain or evidence of a cardiac history. Cardiac aetiology may apply outside of these age ranges in the presence of cardiac symptoms, definitive recent cardiac history and / or ECG changes consistent with a cardiac aetiology[1]. Cases with age or aetiology missing were included in the initial sample (211 cases), with the intention to exclude if age was still unknown or aetiology could not be identified as presumed cardiac after linkage with QHAPDC data. This resulted in a total of 32,557 cases.

The QAS Information Support, Research and Evaluation Unit (ISREU) provided the patient identifier variables of the sample from the QAS OHCA database (unique identifier, eARFnumber, case date, call received time, surname, forename, DOB, gender, patient address, destination) to the Data Linkage Unit (DLU) within Queensland Health. The DLU used specialised linkage software which applies deterministic and probabilistic methodologies, as well as manual clerical reviews where required. The linkage methodology used by the Data Linkage Unit is robust, and undergoes a series of quality assurance checks. For further detail, interested readers are referred to the Queensland Data Linkage Framework [1].

All QAS OHCA Registry cases (32,557) had linkage attempted with the RG Death Registry, to create one de-identified dataset comprising successfully linked RG Death Registry records (29,182). Only cases coded as a resuscitation attempt within the QAS OHCA Registry (16,358) had linkage attempted with QHAPDC, to create another de-identified dataset comprising successfully linked QHAPDC records (4,799). Attempted linkage with QHAPDC for cases not coded as a resuscitation attempt by QAS would have been futile, as these patients would not have been transferred to hospital care. Linkage was undertaken with date boundaries of 1st Jan 2002 – 2nd Jan 2016, in order to capture patient data up to 366 days post event and to calculate outcomes up to 365-day survival.

These two de-identified datasets were provided by the Data Linkage Unit separately to the primary researcher, with eARF number and the unique identifier from the QAS OHCA database appended for merging purposes. The primary researcher merged both datasets with QAS OHCA Registry records (Appendix I – Data management).

One final dataset of QAS OHCA Registry cases was created, appended with successfully linked records. This included QAS OHCA Registry cases linked with records only from RG Death Registry, cases linked with records only from QHAPDC, and cases linked with records from both or neither.

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[1] Queensland Data Linkage Framework:
https://www.health.qld.gov.au/__data/assets/pdf_file/0030/150798/qlddatalinkframework.pdf.

Data were transferred between the QAS ISREU, the DLU and the primary researcher as password protected excel files. These files were changed into SPSS format by the primary researcher for purposes of merging, cleaning, recoding and analysis.

QAS duplicates and patients with multiple presentations

Of the 29,182 RG Death Registry records successfully linked with QAS records, 96 duplicate cases were identified by the Data Linkage Unit. A patient ID variable was provided on the linked RG Death Registry records to identify the duplicate cases. These were individually checked manually and 36 records were identified as true duplicates within the initial sample (identified by identical or near (within 2 days) case dates). These were removed leaving 32,521 cases in the sample. The remaining 60 duplicates were identified as re-presentations of the same patient (59 patients with a 2^{nd} presentation, and 1 patient with a 3^{rd} presentation), so remained in the sample. A variable called 'Presentation' was constructed to identify these. The QAS dataset and death registration data were then merged by the QAS OHCA unique identifier and eARF.

Multiple hospital admissions

Of the 4,799 QHAPDC records successfully linked with QAS OHCA registry records, 4,327 were identified as primary cases and 472 represented multiple admissions of the same patient for the same case (identified by duplicate checks in SPSS of eARF and QAS OHCA unique identifier). For example, some patients were transferred to different departments / hospitals so had two or more QHAPDC linkage records for the same occurrence of OHCA. These 472 records were recoded as additional variables under the appropriate case using the Restructure Data Wizard in SPSS. The order of each admission was recorded chronologically as per the 'Separation ID' variable provided within QHAPDC. Of the 4,327 records identified as primary cases, 4,324 were identified as true individual cases and 3 as QAS duplicates (already identified via the RG Death Registry data and excluded), leaving 4324 individual cases (some with multiple QHAPDC records). All 4,324 individual cases were successfully merged with QAS records by eARF and QAS OHCA unique identifier.

Cases with unknown age or aetiology

There were 210 cases with an unknown age in the initial sample dataset. Of these, one was in the group identified as a duplicate by linkage with the RG Death Registry (so already deleted), eight were identified as adults so remained in the sample, two were identified as under 18 and the remaining 199 still had an unknown age, so were deleted from the sample. The one case with an unknown aetiology in the initial sample was not successfully linked to either QHAPDC or RG Death Registry so was deleted from the sample.

Further exclusions informed by the linkage process are as follows: 36 cases identified as true duplicates within the QAS dataset, two cases identified as under 18yrs of age, 199 cases of unknown age post-linkage, and one case with unknown aetiology post-linkage. For further details see Appendix I (Data management).

The final sample consisted of 32,319 cases, 4,324 of which were merged with individual or multiple QHAPDC records and 29,087 of which were merged with RG Death Registry Data (Figure A).

There are a reduced number of records merged than records linked for the following discussed reasons: Identification of QAS duplicates; multiple QAS presentations for some patients; and multiple hospital admissions associated with the same case.

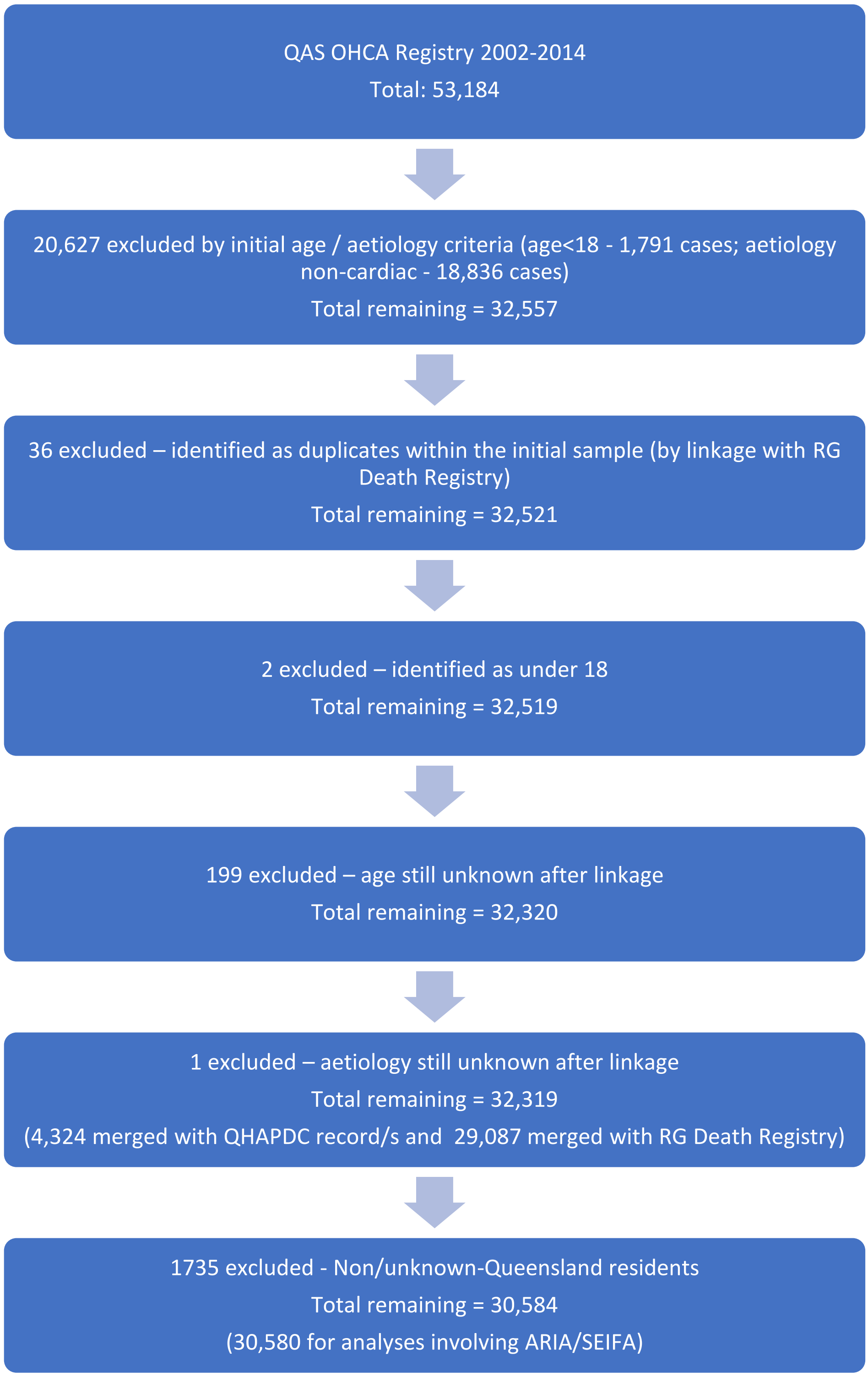

Figure A: Case identification process

Data linkage contributed to this study in two main ways, as follows:

1) The provision of additional variables which are unavailable from the QAS OHCA Registry - These include hospital admission status, length of stay, discharge status, and the long-term survival outcomes specifically required for this study. Analyses of patient status and outcome past the point of hospital arrival would have been impossible without data linkage;

2) The provision of multiple sources of information for the same variable – These include gender, age and residential postcode. Therefore, data linkage increased the completeness and accuracy of the final dataset used for analyses and therefore improved the study's validity. For example, if the QAS OHCA Registry alone were used, residential postcode would have only been available in 66% of cases (21335/32319), whereas with data linkage 97% of cases (31220/32319) had residential postcode assigned.

Data linkage cannot ensure the completeness of the case identifying dataset, i.e., cannot ensure all cases of adult OHCA of cardiac aetiology in Queensland (2002-2014) were captured. Nevertheless and notably, the case identifying dataset (QAS OHCA registry) has rigorous collection and reconciliation processes [1] to address some potential weaknesses of routine ambulance data collections, indicating close to 100% case capture.

3.5 Data cleaning and recoding

The methods used for data cleaning and re-coding (including transforming and construction) firstly relied (where reasonable and available) on the accuracy of RG Death Registry data, followed by QHAPDC data, followed by QAS data. See Appendix I for further details, variable specific methods and assumptions. The key variables in the thesis are summarised below. Other variables are described in Appendix H.

Geographical remoteness and socio-economic status (SES)

The potential to capture residential postcode exists in pre-hospital records, but this information is often missing due to the fact that the event may not happen at home, these patients are usually unconscious and bystanders may not have the information, combined with the short window paramedics have to collect information and their justifiable clinical focus.

In this thesis, data linkage allowed the capturing of residential postcode that is routinely recorded within hospital and death records. Residential status was required to enable exclusion of non-residents of Queensland (or those with unknown residential status) from incidence rate calculations, as only Queensland residents were included in incidence rate calculations. Non-Queensland residents or cases with unknown residential status were excluded. Additionally, the patient's residential postcode was used to ascertain socio-economic status and geographical remoteness.

For patient residential postcode, the primary source was the RG Death Registry, the secondary source was QHAPDC and the tertiary source was QAS OHCA Registry.

The geographical remoteness and SES variables were constructed for known Queensland residents using residential postcode. This was informed using ABS data: 1) By matching ARIA (Accessibility/Remoteness Index of Australia) categories[2, 3] with postcode as per 2011[4] and SEIFA (Socioeconomic Indexes For Areas) categories[5] with postcode as per 2011[6]; and 2) Writing two separate syntax to reflect this.

There were multiple ARIA classifications for some postcodes, so the category with the largest population allocated to it for that postcode was used as definitive. Postcodes 4001 and 4004 were not allocated a remoteness classification due to their previous use as PO Box postcodes. They are now used for some residential addresses meeting criteria for the allocation of 'Major cities', so this was applied. For ARIA, there were 20 cases for which the postcodes were not allocated a category, so remained 'unknown'. For SEIFA, there were 42 for which the postcodes were not allocated a category, so remained 'unknown'.

SEIFA was used to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [5]. SEIFA was coded into deciles. Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage.

ARIA was used to establish geographical remoteness. ARIA was developed by the National Centre for the Social Applications of Geographic Information Systems (GISCA)[2]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories[3]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+).

3.6 Additional analyses

Additional analyses were completed to determine if the postcode of the case location (where QAS attended the incident) would have been suitably reflective of the residential postcode that was obtained from either QHAPDC or RG Death Registry data sources.

There were 28 157 / 30 584 (92.06%) cases that have the same geographical remoteness category when calculated from the case location postcode (QAS dataset only) and residential postcode (all datasets) separately. If only case location postcode had been used to determine geographical remoteness, 20 cases that currently have an unknown status would have a known postcode (and ARIA) and 1348 cases that currently have a postcode (and ARIA) would have an unknown status (and ARIA).

There were 26 279 / 30 584 (85.92%) cases that have the same SES category when calculated from the case location postcode (QAS dataset only) and residential postcode (all datasets) separately. If case location postcode had been used to determine SES, 33 cases that currently have an unknown status would have a known postcode (and SEIFA) and 1389 cases that currently have a postcode (and SEIFA) would have an unknown status (and SEIFA).

This highlights the utility of linking pre-hospital data to other data sources to obtain information on important variables such as socio-economic status and rurality.

Population data

Population data were obtained from the Australian Bureau of Statistics (ABS) to calculate incidence rates. Population data for each calendar year between 2002 and 2014 were obtained for each year of age for males and females separately.

Population data by ARIA, SEIFA or postcode were not available in this format (i.e., by year of age for males and females separately, for every calendar year of the data collection period). For analyses involving ARIA and SEIFA, Estimated Residential population (ERP) data were obtained for each calendar year by gender and age-group (5-year intervals), for each statistical local area (SA2) in Queensland[7]. These data were converted into ARIA and SEIFA categories as follows.

Remoteness (ARIA)

Each SA2 in Queensland (of which there are 526) was allocated an ARIA remoteness category using ABS population weighted allocations to SA2 as per 2011[4]. There were 76/526 SA2s in Queensland with two or more ARIA classification codes allocated to them (as percentages of the population). For these, the remoteness category with the largest proportion of population in that SA2 was allocated. The SA2s were then re-organised into groups of remoteness category along with their relevant population data by age through a series of spreadsheets. This allowed the recalculation of population data by remoteness category. This process was undertaken independently for each gender (male, female and all persons) for every calendar year (2002-2014).

Socio-economic status (SEIFA)

Similarly, each SA2 in Queensland (of which there are 526) was allocated a SEIFA decile using ABS determined allocations as per 2011[6]. Some SA2s (14) have no SEIFA code allocated, likely due to the very low populations. These were handled as an additional category called ‘unknown’. The SA2s were then re-organised into groups of SEIFA decile along with their relevant population data by age through a series of spreadsheets. This allowed the recalculation of population data by SEIFA decile. This process was undertaken independently for each gender (male, female and all persons) for every calendar year (2002-2014).

Outcomes

Different outcomes are used in different Chapters of this thesis. For clarification, the sample and outcomes used in each Chapter (and publication) are described below.

Chapters 4 and 5 (publications 3 and 4) – Pre-hospital Outcomes of Adult OHCA in Queensland, Australia

Sample: All cases of adult OHCA of presumed cardiac aetiology in Queensland residents recorded within the QAS OHCA Registry between 1st Jan 2002 - 31st Dec 2014

There are four separate, mutually exclusive outcomes:

1. No resuscitation (No-Resus) – cases for which a resuscitation attempt was not made by QAS
2. Resuscitation, no ROSC (No-ROSC) – cases for which a resuscitation attempt was made by QAS, but ROSC was not achieved
3. Resuscitation, ROSC not to ED (Unsustained-ROSC) - cases for which a resuscitation attempt was made by QAS, ROSC was achieved but it was not sustained to hospital arrival
4. Resuscitation, ROSC to ED (Sustained-ROSC) - cases for which a resuscitation attempt was made by QAS, ROSC was achieved and sustained to hospital arrival

Chapter 6 (publication 5) – Long-term Outcomes of Adult OHCA in Queensland, Australia

Sample: All cases of adult OHCA of presumed cardiac aetiology in Queensland residents recorded within the QAS OHCA Registry between 1st Jan 2002 - 31st Dec 2014 and survived to hospital admission or beyond

There are three separate, mutually exclusive outcomes:

1. Survival to admission-29 days (Surv<30days) - cases in which the patient survived to hospital admission, but not beyond 29 days
2. Survival to 30-364 days (Surv30-364days) – cases in which the patient survived to 30 days, but not more than 364 days
3. Survival to 365 days or more (Surv365days+) – cases in which the patient survived to 365 days or more

Chapter 7 (publication 6): - Pre-hospital Predictors of Survival from Adult OHCA

Sample: All cases of adult OHCA of presumed cardiac aetiology in Queensland residents recorded within the QAS OHCA Registry between 1st Jan 2002 - 31st Dec 2014 and received a resuscitation attempt by QAS Paramedics

There are four separate, mutually exclusive outcomes:

1. No ROSC to/in ED (-ROSC to/in ED) – cases for which ROSC was not achieved, or ROSC was achieved but it was not sustained to ED. Additionally in cases that were transported, ROSC was not achieved in ED
2. ROSC to/in ED (+ROSC to/in ED) – cases for which ROSC was achieved and sustained to hospital arrival and/or ROSC was achieved in ED, but the patient died in 29 days or less
3. Survival to 30-364 days (Surv30-364days) – cases in which the patient survived to 30 days, but not more than 364 days
4. Survival to 365 days or more (Surv365days+) – cases in which the patient survived to 365 days or more

The shorter-term outcomes were selected to differentiate between routinely reported predictors of favourable longer-term outcomes – i.e., resuscitation attempt, any ROSC, ROSC sustained to or in ED and survival to hospital admission. Furthermore, all outcomes are routinely reported outcomes from OHCA[8].

3.7 Analyses

Analyses are described in detail in the relevant section within the Methods of each Chapter. A brief overview is presented here.

Microsoft Excel (16.12) and STATA (15.1; StatCorp, College Station, Tx, USA) were used to calculate crude and age-standardised population-based incidence rates by gender, age-group, geographical remoteness, socio-economic status and outcome (pre-hospital and long-term) (Chapters 4 -6). STATA (15.1; StatCorp, College Station, Tx, USA) was also used to analyse temporal trends in incidence rates using Poisson regression or negative binomial distribution regression as appropriate (Chapters 5 and 6). SPSS (IBM, Armonk, NY, USA) was used for descriptive analyses and in Chapter 7 to build a model identifying predictors of outcome (multinomial logistic regression).

3.8 Chapter Summary

This Chapter summarises the methods used for the remainder of the thesis (Chapters 4-7). Data linkage allowed the collation of a large, complete and accurate dataset which provided the basis for some detailed data analyses that would not have been otherwise possible. The specific methods for each individual study are detailed in the relevant Chapters.

3.9 References

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Chapter 4: Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia

4.1 Overview

This Chapter comprises the third publication in the thesis, and the first in a series of two exploring the epidemiology of outcomes of adult OHCA of presumed cardiac aetiology, attended by QAS paramedics in Queensland. It is the first of three Chapters addressing aim 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia)* of the thesis. Specifically, in this paper, incidence of adult OHCA in Queensland by age, gender, geographical remoteness and socio-economic status are presented. Incidence rates are reported overall and by pre-hospital outcome (described below).

At the time of conception of this research, there were limited previous studies and none in Australasia that described population-based incidence rates of OHCA by pre-hospital outcome. Outcomes of OHCA are largely reported as proportions of the OHCA population. Incidence accounts for changes in population demographics, so is a more informative measure than proportions alone and is consequently preferable to benchmark current status and inform strategy development and service provision. Therefore, this is an informative and important addition to the literature.

All cases of adult OHCA of presumed cardiac aetiology in residents of Queensland attended by QAS paramedics in Queensland are included in this study (N=30,560). There are four mutually exclusive pre-hospital outcomes:

- No resuscitation (No-Resus): This group received no resuscitation attempt by QAS paramedics. This is the least preferred outcome

- No return of spontaneous circulation (No-ROSC): This group received a resuscitation attempt by QAS paramedics, but pre-hospital ROSC was not achieved at any stage
- ROSC not sustained to hospital (Unsustained-ROSC): This group received a resuscitation attempt by QAS paramedics, pre-hospital ROSC was achieved but it was not sustained to hospital
- ROSC sustained to hospital (Sustained-ROSC): This group received a resuscitation attempt by QAS paramedics, pre-hospital ROSC was achieved and it was sustained to hospital. This is the most preferred outcome

Figure A contextualises this Chapter in the thesis.

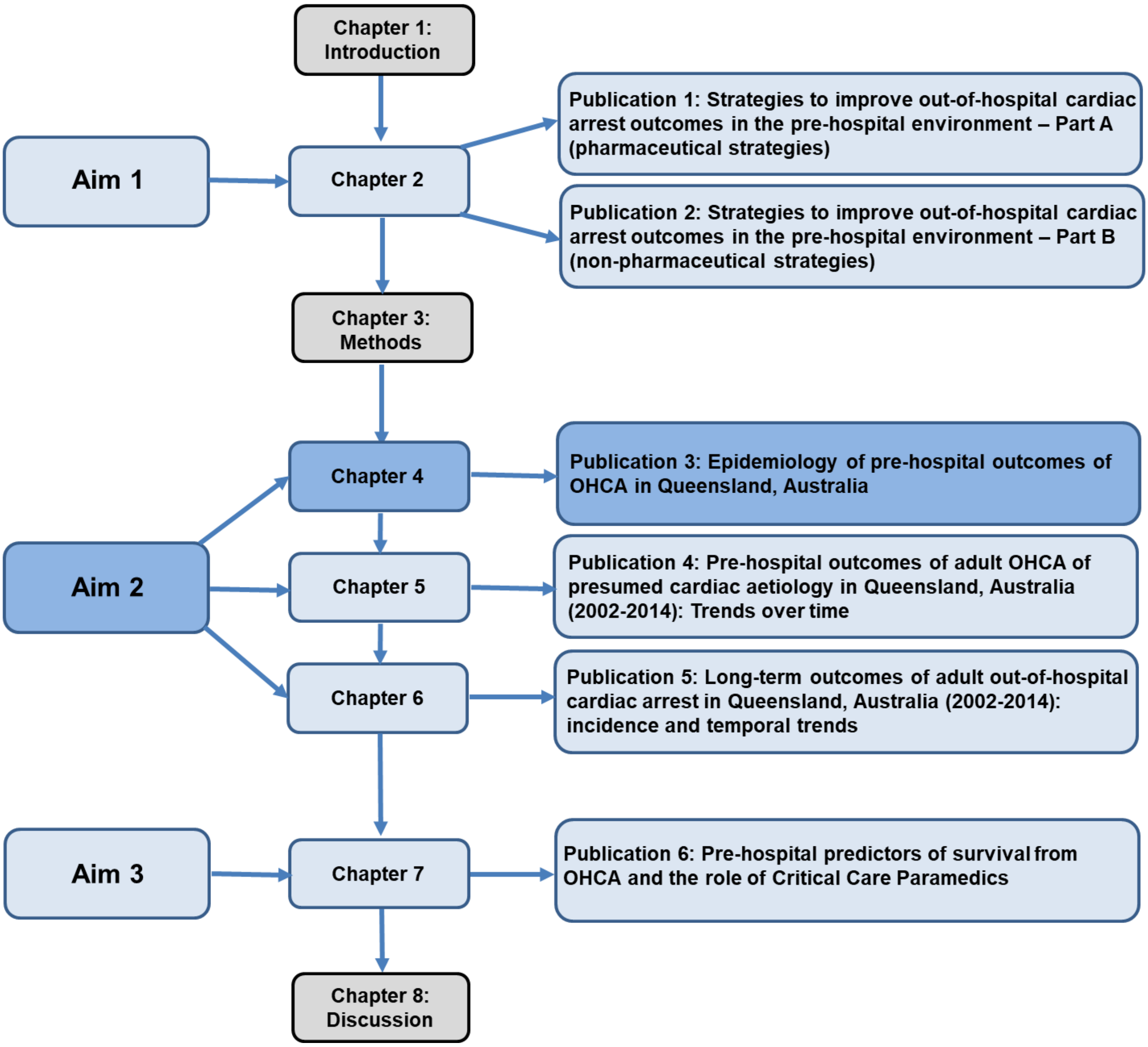

Figure A: Conceptual model of thesis – Aim 2, Chapter 4, Publication 3

4.2 Manuscript

This Chapter comprises a manuscript that has been published in a peer-reviewed journal, and is inserted as a PDF in the format published by the journal:

Pemberton K, Bosley E, Franklin RC and Watt K. Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia. *Emergency Medicine Australasia*. 2019; **31**: 821-9.

Supplementary material supporting this article is presented prior to the Chapter summary.

EMA Emergency Medicine Australasia

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ORIGINAL RESEARCH

Epidemiology of pre-hospital outcomes of out-of-hospital cardiac arrest in Queensland, Australia

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Abstract

Objective: To describe incidence in pre-hospital outcomes of adult out-of-hospital cardiac arrest (OHCA) of presumed cardiac aetiology, attended by Queensland Ambulance Service (QAS) paramedics between 2002 and 2014, by age, gender, geographical remoteness and socio-economic status.

Methods: The QAS OHCA Registry was used to identify cases, which was then linked with Queensland Hospital Admitted Patient Data Collection and Queensland Death Registry. Population data were obtained for each calendar year by age and gender from the Australian Bureau of Statistics in order to calculate incidence rates. Four mutually exclusive pre-hospital outcomes were analysed: (i) no resuscitation (No-Resus); (ii) resuscitation, no pre-hospital return of spontaneous circulation (No-ROSC); (iii) resuscitation, pre-hospital return of spontaneous circulation not sustained to hospital (Unsustained-ROSC); and (iv) resuscitation, pre-hospital return of spontaneous circulation sustained to hospital (Sustained-ROSC).

Results: Over the 13 years, there were 30 560 OHCA cases for analyses. Incidence was significantly greater in males than females and incrementally increased with age, for each outcome. Incidence of total OHCA events generally increased as remoteness increased (major cities: 72.39 per 100 000 [95% CI 71.35–73.45]; very remote: 87.01 per 100 000 [95% CI 78.03–95.98]). There was an inverse association between incidence of OHCA events and socio-economic status (SEIFA 1 and 2: 81.34 per 100 000 [95% CI 79.28–83.40]; SEIFA 9 and 10: 61.57 per 100 000 [95% CI 59.67–63.46]).

Conclusion: Rural-specific strategies should be continued. Prevention and management strategies for OHCA targeting lower socio-economic groups require focus.

Key words: *cardiac arrest, emergency medical services, epidemiology, pre-hospital.*

Key findings

- Incidence of OHCA events generally increased as remoteness increased.
- An inverse association between incidence of OHCA events and socio-economic status.
- An incremental increase in incidence of OHCA events and all outcomes with age.

Introduction

Incidence of out-of-hospital cardiac arrest (OHCA) differs globally.[1,2] In Australia, there are approximately 25 000 OHCAs annually.[3]

Pre-hospital outcomes from OHCA, such as commencement of a resuscitation attempt and return of spontaneous circulation (ROSC), are key performance indicators for ambulance services. Outcomes are routinely reported as proportions of the OHCA population.[2,4–7] However, population-based incidence of OHCA outcomes provides a more meaningful public health measure. Reporting incidence is a more informative method to benchmark current status and guide future direction because it accounts for changes in population demographics (such as age and gender) over time.

There are limited published studies where population incidence rates of OHCA by outcome are described. The EuReCa ONE study reported OHCA outcomes on a sample of 10 682 cases of OHCA in 27 European countries in 1 month. Population incidence rates (per 100 000 per year) were reported by country for resuscitation attempts (range 19–104), ROSC (range 6–32), survival (range 0.2–17.3) and survival in bystander witnessed events of suspected cardiac aetiology with an initial shockable rhythm (range 0.1–6.3).[8] There were no further demographic subgroup analyses.

Other studies reporting incidence have focused on trends in rates of OHCA over time, but not by outcome.[9–14] Four of these studies show declining incidence rates over time in patients with a shockable rhythm who received a resuscitation attempt.[9–12] While the shockable rhythm receiving a resuscitation attempt subgroup could be

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considered an outcome of OHCA, only one study reported on the whole population and/or other subgroups.[12] The additional subgroups examined were pulseless electrical activity and asystole. The study[12] also examined outcome, but by proportion of the initial population only (not incidence). Two of the studies focusing on trends were a study in Western Australia (1997–2010)[13] and one in Queensland (2002–2014).[14] As well as trends over time, they both reported mean annual incidence rates per 100 000 of the population as: 69.8 and 85.4 (age-standardised), 60.2 and 78.2 (crude) and 355.1 and 322.54 (age-standardised in age 65+ years), respectively. Neither study reported results by outcome.

Geographical remoteness and socio-economic status (SES) are known to impact on healthcare and outcomes, such that Australians living in rural and remote areas have lower life expectancy and higher rates of disease and injury than people living in major cities.[15] To the authors' knowledge, there are no studies where incidence of outcomes from OHCA are examined in relation to SES. There are several studies that have explored outcomes from OHCA by remoteness, but incidence of outcomes has not been reported.[2,16–19] One Australian study reported crude and age-adjusted incidence of all OHCA cases and those with a resuscitation attempt by population density, rather than remoteness specifically.[20] The present study aims to address these gaps. Understanding outcomes from OHCA is important to ambulance services when developing future strategies for improvements.[14,21] There is current emphasis on measuring the size of the health gap between groups,[15] and reporting incidence of outcome by remoteness and SES will contribute to better inform the specifics of any differences found and enable some evaluation of previously implemented strategies.

The aim of the present study is to identify incidence of pre-hospital outcomes in adult OHCA of presumed cardiac aetiology attended by Queensland Ambulance Service (QAS) paramedics between 2002 and 2014, by age, gender, remoteness and SES. This is in line with step one of the 10 Steps to Improve Cardiac Arrest Survival by the Global Resuscitation Alliance, which highlights the importance of data capture, analysis and application.[22]

Methods

In this retrospective cohort study, data from three sources were linked: (i) QAS OHCA Registry; (ii) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and (iii) Queensland Registrar General Death Registry.

The QAS OHCA Registry[23] was used to identify cases for linkage. Study inclusion criteria were: adults (≥18 years) and resident in Queensland who experienced a cardiac arrest of presumed cardiac aetiology and were attended by QAS paramedics between 1 January 2002 and 31 December 2014. Data were linked to QHAPDC and the Death Registry via the Data Linkage Unit (DLU), Queensland Health, using specialised linkage software that applies deterministic and probabilistic methodologies, supplemented by manual clerical reviews where required. Presumed cardiac aetiology is allocated in the presence of cardiac symptoms or history and/or in males ≥40 years and females ≥50 years old, when there is no evidence to suggest another classification is more appropriate.[23]

Residential postcode was used to ascertain SES (via Socio-Economic Indexes for Areas [SEIFA], specifically Index of Relative Socio-Economic Advantage and Disadvantage, with higher deciles reflecting higher relative advantage)[24] and geographical remoteness (via Accessibility/Remoteness Index of Australia [ARIA], categorised as major city, inner regional, outer regional, remote, or very remote).[25,26]

Population data were obtained for each calendar year between 2002 and 2014 by age and gender from the Australian Bureau of Statistics (ABS) in order to calculate incidence rates.[27] The ABS provides population data for each age year, from 1901 onwards. For analyses involving ARIA and SEIFA, population data by statistical local area 2 (SA2) and age group were obtained for each calendar year but were only available for adults 20+ years. Hence, cases were excluded from any analyses involving ARIA and SEIFA if age <20 years, or if an ARIA/SEIFA category could not be established from postcode (Fig. 1).

Four mutually exclusive pre-hospital outcomes were analysed. These were: (i) no resuscitation (No-Resus); (ii) resuscitation, no pre-hospital ROSC (No-ROSC); (iii) resuscitation, pre-hospital ROSC not sustained to hospital (Unsustained-ROSC); and (iv) resuscitation, pre-hospital ROSC sustained to hospital (Sustained-ROSC). These outcomes are routinely highlighted as important reportable outcomes[28] and predictors of favourable longer-term outcomes.

Analyses

Analyses were undertaken using Microsoft Excel (16.12) and STATA (15.1; StataCorp, College Station, TX, USA). Incidence rates for total OHCA events and for each outcome were calculated by age-group and gender. These same rates were calculated stratified by remoteness and SES. Age-standardised rates (directly standardised to the Australian population 2001) were calculated for each outcome and for total OHCA events for all cases, and separately by gender, then stratified by SES and remoteness. Relative risks (RRs) and 95% CIs were then calculated to quantify risk factors for total OHCA and by outcome.

Ethics approval

Ethical approval for this study was obtained from Prince Charles Hospital Human Research Ethics Committee (approval number 15/QPCH/265), and from James Cook University Human Research Ethics Committee (approval number H5752). Access to confidential data was obtained via the Public Health Act through Queensland Health (approval number RD006708) and QAS Commissioner approval was obtained.

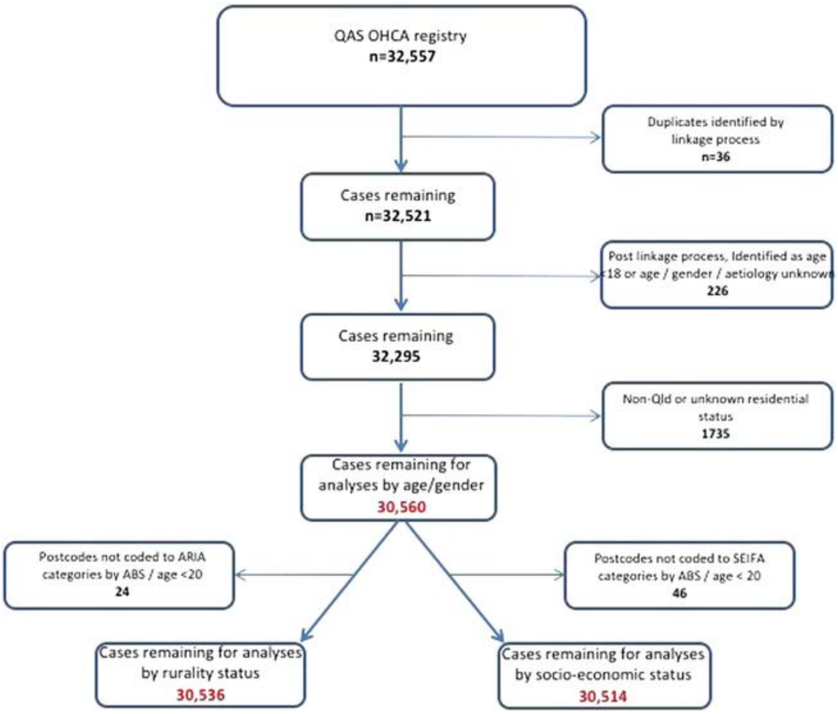

Figure 1. *Flowchart to show inclusion and exclusion criteria for sample data. ABS, Australian Bureau of Statistics; OHCA, out-of-hospital cardiac arrest; QAS, Queensland Ambulance Service.*

Results

Over the 13 year study period, 32 557 cases from the QAS OHCA Registry met inclusion criteria; 1997 cases were excluded (Fig. 1), leaving 30 560 cases for analyses. There were 30 536 cases for analyses involving geographical remoteness (missing = 24), and 30 514 cases for analyses involving SES (missing = 46).

Table 1 shows the age- and gender-specific annual incidence rates, as well as age-standardised rates for each outcome and for OHCA events overall, between 2002 and 2014. Table 2 displays gender-specific incidence rates stratified by geographical remoteness, and SES. Table 3 shows relative risks and 95% CIs.

Annual crude incidence rate of total OHCA events was 73.95 (95% CI 73.12–74.78) per 100 000 per annum; 37.31 (95% CI 36.72–37.90) for No-Resus, 25.98 (95% CI 25.48–26.47) for No-ROSC, 1.64 (95% CI 1.51–1.76) for Unsustained-ROSC and 9.03 (95% CI 8.74–9.32) for Sustained-ROSC (Table 1).

Age/gender

Crude incidence of total OHCA events was higher in males (98.14; 95% CI 96.78–99.49) than females (50.32; 95% CI 49.36–51.28). This pattern was repeated for each outcome (Table 1). Typically, rates were twice as high in males than females (Table 3), except for OHCA events resulting in No-Resus, where incidence was 1.7 times higher in males. This effect was even more pronounced in age-standardised incidence rates. Examination of age-specific rates showed the same pattern, except in OHCA resulting in No-ROSC in those aged 18–24 years, where the incidence was higher in females than males, although non-significantly.

Total OHCA incidence increased incrementally with age, from 0.59 per 100 000 per annum in 18–24 years, to 660.97 per 100 000 per annum in those aged 85+ years. This was true for every outcome in both females and males (Table 1). The only exception was OHCA events resulting in Unsustained-ROSC among females, where the rate decreased from 6.13 per 100 000 per annum in 75–84 years to 5.34 in females aged 85+ years.

Geographical remoteness and socio-economic status

Figure 2 shows annual crude incidence of total OHCA events stratified by geographical remoteness. Incidence of total OHCA events are displayed in Table 2. Compared with major cities, total OHCA incidence was significantly higher in inner regional (RR 1.22; 95% CI 1.19–1.25), outer regional (RR 1.10; 95% CI 1.07–1.14) and very remote areas (RR 1.20; 95% CI 1.08–1.33) (Table 3).

This pattern was also observed for OHCA resulting in No-Resus and No-ROSC (Table 3). In OHCA resulting in Unsustained-ROSC, incidence in inner regional areas was approximately the same as in major cities, and while incidence was lower in outer regional, remote and very remote areas, it was not significantly lower. In OHCA events resulting in Sustained-ROSC, a similar pattern was observed, except that incidence was significantly lower in remote areas than in major cities (Table 3). Incidence of total OHCA events in remote areas was significantly lower than in major cities (RR 0.86; 95% CI 0.78–0.96). This was also true for OHCA events resulting in No-ROSC, and events resulting in Sustained-ROSC.

When stratified by remoteness, total OHCA incidence was significantly greater in males than females, for each remoteness category. This was also true for OHCA events resulting in No-Resus and No-ROSC. For OHCA events resulting in Unsustained-ROSC and Sustained-ROSC in remote and very remote areas, incidence remained higher in males than females, but not significantly (Table 2).

There was an inverse association between SES and incidence of overall OHCA (Tables 2,3; Fig. 2). Incidence of total OHCA events was significantly higher in areas characterised by lower relative advantage (SEIFA 1 and 2: 81.34; 95%CI 79.28–83.40) than in areas of higher advantage (SEIFA 9 and 10: 61.57; 95% CI 59.67–63.46; RR 0.76; 95% CI

TABLE 1. *Annual adult out-of-hospital cardiac arrest incidence rates and 95% confidence intervals (age- and gender-specific and age-standardised) by pre-hospital outcome in Queensland, Australia (per 100 000), 2002–2014*

	Pre-hospital outcome														
	No-Resus			No-ROSC			Unsustained-ROSC			Sustained-ROSC			Total events		
Age group (years)	Female (n = 5784)	Male (n = 9634)	Total (n = 15 418)	Female (n = 3284)	Male (n = 7450)	Total (n = 10 734)	Female (n = 219)	Male (n = 457)	Total (n = 676)	Female (n = 1229)	Male (n = 2503)	Total (n = 3732)	Female (n = 10 516)	Male (n = 20 044)	Total (n = 30 560)
18–24, n = 32	0.08 (0.00–0.18)	0.29 (0.09–0.49)	0.19 (0.07–0.30)	0.26 (0.07–0.46)	0.18 (0.02–0.34)	0.22 (0.13–0.39)	0	0	0	0.11 (0.00–0.24)	0.26 (0.07–0.44)	0.19 (0.10–0.34)	0.45 (0.20–0.71)	0.73 (0.41–1.05)	0.59 (0.39–0.80)
25–34, n = 123	0.21 (0.06–0.35)	0.597 (0.35–0.84)	0.40 (0.26–0.55)	0.29 (0.12–0.46)	1.25 (0.89–1.60)	0.77 (0.57–0.96)	0.03 (0.00–0.08)	0.10 (0.00–0.21)	0.07 (0.01–0.12)	0.18 (0.05–0.32)	0.55 (0.31–0.78)	0.36 (0.23–0.50)	0.70 (0.44–0.97)	2.49 (1.99–2.99)	1.60 (1.32–1.88)
35–44, n = 913	0.80 (0.52–1.08)	7.52 (6.66–8.37)	4.12 (3.68–4.57)	1.08 (0.76–1.40)	8.74 (7.82–9.67)	4.87 (4.38–5.36)	0.13 (0.02–0.24)	0.64 (0.39–0.89)	0.38 (0.24–0.52)	0.95 (0.65–1.25)	3.43 (2.85–4.01)	2.18 (1.85–2.50)	2.96 (2.42–3.49)	20.32 (18.91–21.74)	11.55 (10.80–12.30)
45–54, n = 3188	8.61 (7.67–9.55)	29.63 (27.93–31.46)	19.03 (18.04–20.02)	6.04 (5.25–6.83)	26.39 (24.79–28.12)	16.13 (15.22–17.05)	0.40 (0.20–0.60)	1.36 (0.98–1.74)	0.88 (0.66–1.09)	3.15 (2.59–3.72)	10.76 (9.73–11.85)	6.93 (6.33–7.53)	18.20 (16.84–19.57)	68.31 (65.63–70.98)	42.96 (41.47–44.46)
55–64, n = 5485	24.10 (22.35–25.86)	60.95 (58.18–63.73)	42.66 (41.01–44.30)	14.82 (13.44–16.20)	50.35 (47.83–52.87)	32.71 (31.27–34.15)	1.34 (0.92–1.75)	3.39 (2.74–4.05)	2.37 (1.98–2.76)	7.68 (6.69–8.67)	18.64 (17.10–20.17)	13.20 (12.28–14.11)	47.94 (45.46–50.42)	133.33 (129.23–137.44)	90.93 (88.53–93.34)
65–74, n = 7062	58.05 (54.65–61.46)	122.76 (117.81–127.71)	90.41 (87.41–93.42)	35.86 (33.18–38.54)	94.45 (90.10–98.79)	65.16 (62.61–67.71)	2.86 (2.10–3.61)	5.77 (4.69–6.84)	4.31 (3.66–4.97)	14.14 (12.46–15.82)	33.04 (30.47–35.61)	23.59 (22.06–25.12)	110.91 (106.20–115.61)	256.01 (248.86–263.16)	183.47 (179.19–187.75)
75–84, n = 8461	151.13 (144.24–158.02)	260.41 (250.43–270.39)	200.39 (194.51–206.27)	87.02 (81.79–92.24)	184.77 (176.36–193.18)	131.08 (126.32–135.83)	6.13 (4.75–7.52)	11.86 (9.73–13.99)	8.71 (7.49–9.94)	27.89 (24.93–30.85)	54.51 (49.95–59.08)	39.89 (37.27–42.51)	272.17 (262.92–281.42)	511.55 (497.56–525.55)	380.07 (371.91–388.16)
85+, n = 5296	330.51 (314.94–346.07)	502.71 (476.30–529.12	390.02 (376.34–403.69)	152.38 (141.81–162.95)	318.89 (297.86–339.92)	209.92 (199.89–219.96)	5.34 (3.36–7.32)	16.25 (11.50–21.00)	9.11 (7.02–11.20)	41.96 (36.41–47.50)	70.78 (60.87–80.69)	51.92 (46.93–56.91)	530.18 (510.47–549.89)	908.64 (873.14–944.15)	660.97 (643.17–678.77)
Total, n = 30 560	27.68 (26.96–28.39)	47.17 (46.23–48.11)	37.31 (36.72–37.90)	15.71 (15.18–16.25)	36.48 (35.65–37.30)	25.98 (25.48–26.47)	1.05 (0.91–1.19)	2.24 (2.03–2.44)	1.64 (1.51–1.76)	5.88 (5.55–6.21)	12.25 (11.77–12.73)	9.03 (8.74–9.32)	50.32 (49.36–51.28)	98.14 (96.78–99.49)	73.95 (73.12–74.78)
Age-standardised	24.83 (24.02–25.64)	50.06 (48.91–51.21)	36.64 (35.66–37.62)	14.33 (13.71–14.94)	38.21 (37.21–39.22)	25.52 (24.70–26.34)	0.99 (0.82–1.15)	2.33 (2.08–2.57)	1.61 (1.40–1.81)	5.44 (5.06–5.82)	12.57 (11.99–13.14)	8.84 (8.36–9.32)	45.58 (44.48–46.67)	103.17 (101.53–104.82)	72.61 71.23–73.99)

No-Resus, no resuscitation; No-ROSC, resuscitation, no pre-hospital ROSC; Unsustained-ROSC, resuscitation, pre-hospital ROSC not sustained to hospital; Sustained-ROSC, resuscitation, pre-hospital ROSC sustained to hospital

TABLE 2. *Annual adult out-of-hospital cardiac arrest incidence rates and 95% confidence intervals by remoteness, socio-economic status and pre-hospital outcome in Queensland, Australia (per 100 000), 2002–2014†*

	Pre-hospital outcome														
	No-Resus			No-ROSC			Unsustained-ROSC			Sustained-ROSC			Total events		
Geographical remoteness (ARIA)‡	Female (n = 5777)	Male (n = 9628)	Total (n = 15 405)	Female (n = 3282)	Male (n = 7445)	Total (n = 10 727)	Female (n = 219)	Male (n = 456)	Total (n = 675)	Female (n = 1229)	Male (n = 2500)	Total (n = 3729)	Female (n = 10 507)	Male (n = 20 029)	Total (n = 30 536)
Major cities, n = 1794	27.98 (27.06–28.90)	43.49 (42.32–44.66)	35.55 (34.81–36.29)	15.63 (14.95–16.32)	36.25 (35.18–37.32)	25.69 (25.06–26.32)	1.11 (0.92–1.29)	2.37 (2.09–2.64)	1.72 (1.56–1.89)	6.11 (5.68–6.54)	12.91 (12.27–13.55)	9.43 (9.05–9.81)	50.84 (49.60–52.08)	95.02 (93.28–96.75)	72.39 (71.34–73.45)
Inner regional, n = 7108	32.21 (30.46–33.95)	59.78 (57.39–62.18)	45.87 (44.39–47.35)	17.96 (16.66–19.26)	43.12 (41.08–45.15)	30.42 (29.22–31.63)	1.30 (0.95–1.66)	2.36 (1.88–2.83)	1.83 (1.53–2.12)	6.54 (5.76–7.33)	13.82 (12.66–14.97)	10.14 (9.45–10.84)	58.02 (55.68–60.36)	119.07 (115.68–122.45)	88.26 (86.21–90.31)
Outer regional, n = 4683	27.13 (25.23–29.03)	55.31 (52.65–57.98)	41.50 (39.85–43.15)	16.88 (15.38–18.38)	38.98 (36.74–41.22)	28.15 (26.79–29.50)	0.76 (0.44–1.08)	2.27 (1.73–2.81)	1.53 (1.22–1.85)	5.80 (4.92–6.68)	11.22 (10.02–12.42)	8.57 (7.82–9.31)	50.58 (47.98–53.18)	107.79 (104.07–111.51)	79.74 (77.46–82.03)
Remote, n = 390	24.36 (18.65–30.07)	50.38 (42.78–57.97)	38.37 (33.51–43.24)	11.14 (7.28–14.99)	23.55 (18.36–28.74)	17.82 (14.51–21.14)	0.35 (0.00–1.03)	0.89 (0.00–1.91	0.64 (0.01–1.27)	3.83 (1.57–6.09)	7.45 (4.53–10.37)	5.78 (3.89–7.67)	39.67 (32.39–46.96)	82.28 (72.57–91.98)	62.62 (56.40–68.83)
Very remote, n = 361	27.50 (20.23–34.77)	67.00 (56.06–77.94)	47.96 (41.30–54.63)	22.00 (15.50–28.50)	38.62 (30.31–46.93)	30.61 (25.28–35.93)	1.00 (0.00–2.39)	1.86 (0.04–3.68)	1.45 (0.29–2.60)	3.50 (0.91–6.09)	10.24 (5.96–14.51)	6.99 (4.45–9.53)	54.00 (43.82–64.19)	117.71 (103.21–132.220	87.01 (78.03–95.98)
Socio-economic status (SEIFA)§	Female (n = 5774)	Male (n = 9618)	Total (n = 15 392)	Female (n = 3279)	Male (n = 7440)	Total (n = 10 719)	Female (n = 219)	Male (n = 456)	Total (n = 675)	Female (n = 1229)	Male (n = 2499)	Total (n = 3728)	Female (n = 10 501)	Male (n = 20 013)	Total (n = 30 514)
1 and 2, n = 5974	29.34 (27.60–31.08)	56.92 (54.46–59.37)	42.96 (41.46–44.46)	15.52 (14.25–16.78	39.79 (37.74–41.85)	27.50 (26.30–28.70)	1.00 (0.67–1.32)	2.34 (1.85–2.84)	1.66 (1.37–1.96)	5.86 (5.08–6.64)	12.66 (11.50–13.82)	9.22 (8.52–9.91)	51.72 (49.41–54.03)	111.71 (108.27–115.15)	81.34 (79.28–83.40)
3 and 4, n = 5639	27.25 (25.62–28.88)	47.17 (45.01–49.33)	37.16 (35.80–38.51)	15.73 (14.49–16.97)	35.24 (33.37–37.11)	25.43 (24.31–26.55)	1.02 (0.70–1.34)	2.09 (1.63–2.54)	1.55 (1.27–1.83)	5.91 (5.15–6.68)	10.39 (9.37–11.40)	8.14 (7.51–8.77)	49.91 (47.70–52.12)	94.89 (91.82–97.95)	72.27 (70.39–74.16)
5 and 6, n = 5991	24.46 (23.03–25.90)	43.91 (41.96–45.87)	34.06 (32.85–35.27)	14.00 (12.91–15.08)	32.27 (30.60–33.95)	23.01 (22.02–24.00)	0.84 (0.57–1.10)	1.88 (1.48–2.28)	1.35 (1.11–1.59)	5.31 (4.64–5.98)	11.78 (10.76–12.79)	8.50 (7.90–9.10)	44.61 (42.67–46.55)	89.84 (87.05–92.64)	66.92 (65.22–68.61)
7 and 8, n = 8854	36.37 (34.63–38.11)	57.92 (55.70–60.14)	47.01 (45.60–48.42)	20.86 (19.54–22.17)	49.80 (47.74–51.86)	35.15 (33.93–36.37)	1.64 (1.27–2.01)	3.19 (2.67–3.71)	2.41 (2.09–2.73)	7.64 (6.84–8.43)	17.25 (16.04–18.46)	12.38 (11.66–13.11)	66.50 (64.15–68.85)	128.16 (124.86–131.47)	96.95 (94.93–98.97)
9 and 10, n = 4056	24.51 (22.83–26.18)	36.32 (34.24–38.40)	30.30 (28.97–31.63)	14.47 (13.18–15.76)	29.70 (27.82–31.58)	21.93 (20.80–23.07)	0.83 (0.52–1.14)	1.95 (1.47–2.43)	1.38 (1.10–1.67)	5.51 (4.71–6.30)	10.50 (9.38–11.62)	7.95 (7.27–8.64)	45.32 (43.04–47.60)	78.47 (75.41–81.52)	61.57 (59.67–63.46)

†Cases were excluded from any analyses involving ARIA and SEIFA if age <20 years, or if an ARIA/SEIFA category could not be established from postcode. Hence the column totals in Table 1 and Table 2 are slightly different (see Fig. 1 for further detail). ‡Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA).[25] Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories[26]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+). §SEIFA (Socioeconomic Index For Areas) was used to estimate socioeconomic status in this study – specifically, the Index of Relative Socioeconomic Advantage and Disadvantage.[24] Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage. No-Resus, no resuscitation; No-ROSC, resuscitation, no pre-hospital ROSC; Unsustained-ROSC, resuscitation, pre-hospital ROSC not sustained to hospital; Sustained-ROSC, resuscitation, pre-hospital ROSC sustained to hospital.

TABLE 3. *Relative risk ratios and 95% confidence intervals of adult out-of-hospital cardiac arrest, by pre-hospital outcome, gender, geographical remoteness and socio-economic status*

	Pre-hospital outcome				
	No-Resus (*n* = 15 418)	No-ROSC (*n* = 10 734)	Unsustained-ROSC (*n* = 676)	Sustained-ROSC (*n* = 3732)	Total events (*n* = 30 560)
Gender					
Female	Reference group				
Male	1.70 (1.65–1.76)	2.32 (2.23–2.42)	2.14 (1.82–2.51)	2.08 (1.95–2.23)	1.95 (1.90–2.00)
Geographical remoteness (ARIA)†					
Major cities	Reference group				
Inner regional	1.29 (1.24–1.34)	1.18 (1.13–1.24)	1.06 (0.88–1.28)	1.08 (0.99–1.16)	1.22 (1.19–1.25)
Outer regional	1.17 (1.11–1.22)	1.10 (1.04–1.16)	0.89 (0.71–1.12)	0.91 (0.82–1.00)	1.10 (1.07–1.14)
Remote	1.08 (0.95–1.23)	0.69 (0.58–0.84)	0.37 (0.14–1.00)	0.61 (0.44–0.85)	0.86 (0.78–0.96)
Very remote	1.35 (1.17–1.55)	1.19 (1.00–1.42)	0.84 (0.38–1.88)	0.74 (0.51–1.07)	1.20 (1.08–1.33)
Socio-economic status (SEIFA)‡					
1 and 2	Reference group				
3 and 4	0.86 (0.82–0.91)	0.92 (0.87–0.98)	0.93 (0.73–1.20)	0.88 (0.79–0.98)	0.89 (0.86–0.92)
5 and 6	0.79 (0.75–0.83)	0.84 (0.79–0.89)	0.81 (0.63–1.05)	0.92 (0.83–1.02)	0.82 (0.79–0.85)
7 and 8	1.09 (1.05–1.15)	1.28 (1.21–1.35)	1.45 (1.16–1.81)	1.34 (1.22–1.48)	1.19 (1.15–1.23)
9 and 10	0.7 (0.67–0.75)	0.80 (0.75–0.85)	0.83 (0.63–1.09)	0.86 (0.77–0.97)	0.76 (0.73–0.79)

†Cases were excluded from any analyses involving ARIA and SEIFA if age <20 years, or if an ARIA/SEIFA category could not be established from postcode. Hence the column totals in Table 1 and Table 2 are slightly different (see Figure 1 for further detail). ‡Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by the National Centre for the Social Applications of Geographic Information Systems (GISCA).[25] Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories:[26] major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+). No-Resus, no resuscitation; No-ROSC, resuscitation, no pre-hospital ROSC; Unsustained-ROSC, resuscitation, pre-hospital ROSC not sustained to hospital; Sustained-ROSC, resuscitation, pre-hospital ROSC sustained to hospital.

0.73–0.79). An important exception was within areas defined as high (but not the highest) relative advantage – that is, SEIFA categories 7 and 8, where incidence of total OHCA events was significantly higher than in SEIFA categories 1 and 2 (RR 1.19; 95% CI 1.15–1.23). When stratified by SES, incidence of total OHCA events was significantly greater in males than females, and also for each outcome, for each SEIFA category (Table 3).

The same pattern of decreased OHCA incidence associated with increased SES (except for SEIFA categories 7 and 8), was observed for every outcome except OHCA events resulting in Sustained-ROSC, where the association with SES was less consistent (Table 3). For total OHCA events, and for every outcome separately, the highest incidence rates occurred in areas categorised as high (but not the highest) relative advantage (SEIFA categories 7 and 8).

The same results were observed for gender-specific age-standardised rates stratified by remoteness and SES separately (Table S1).

Discussion

This is the first study known to the authors where incidence of OHCA stratified by outcome has been examined in Australasia. Annual crude and age-standardised incidence of OHCA observed in this study are consistent with the few previous national and international findings where incidence rates are reported; although these are only reported overall, not by outcome.[1,13,14]

Incidence of some outcomes were reported in EuReCA ONE[8] from a larger population than this study, albeit a much shorter time frame (1 month), with a substantially smaller sample. Additionally, incidence by age, gender, remoteness or SES were not reported in EuReCA ONE, nor were age-standardised rates, which is a strength of the current study. Other previous studies have focused on outcomes as

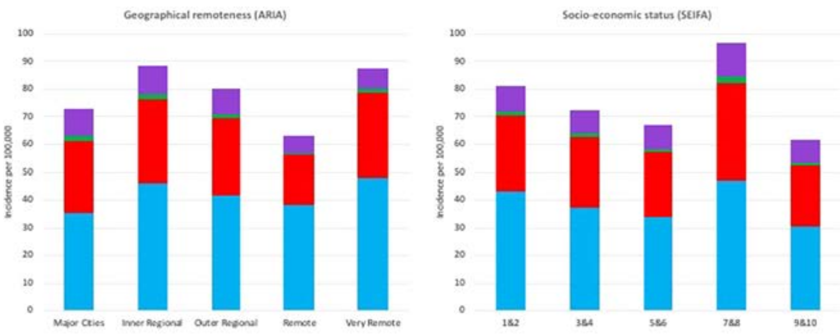

Figure 2. *Annual crude incidence of adult (20+ years) out-of-hospital cardiac arrest of cardiac aetiology for geographical remoteness and socio-economic status, by pre-hospital outcome. (■), No-Resus; (■), No-ROSC; (■), Unsustained-ROSC; (■), Sustained-ROSC.*

proportions among OHCA cases only. This study is a population-based study and provides a more robust measure (incidence).

Geographical remoteness

Geographical remoteness was a novel inclusion in this study. Due to reduced access to healthcare[15] and longer response times, people in rural areas may reasonably be expected to have a greater risk of OHCA and poorer outcomes. The study findings support this (i.e. higher risk of OHCA overall, No-Resus and No-ROSC in inner regional, outer regional and very remote areas [*vs* major cities], and reduced rate of Sustained-ROSC in outer regional, remote and very remote areas). The lowest rates of total events and every outcome (other than No-Resus) were observed in remote areas, which requires further investigation.

Historically, conventional strategies to improve outcomes from OHCA have been less successful in remote locations, presenting a challenge to ambulance services. In recent times, strategies have been implemented in rural areas, such as community engagement to increase rates of bystander CPR, automated external defibrillator use and recruitment of community responders. Trends over time analyses of OHCA outcomes by remoteness would provide important insight on the success of these strategies.[29]

Socio-economic status

In the present study, OHCA incidence mostly decreased as SES increased, which is consistent with evidence that disadvantaged groups experience worse health and greater exposure to risk factors.[15,30] Factors known to cause poorer outcomes from OHCA (such as less bystander CPR and more untreated or unstable chronic disease), are potentially associated with lower SES, although this requires further investigation. Additionally, there were greater differences in the relative risk of preferred outcomes (Sustained-ROSC) and non-preferred outcomes (No-Resus) among people living in areas of higher advantage than in those of lower advantage, indicating that preferred outcomes are more frequent in those of higher SES.

People in areas categorised as high (but not the highest) advantage (SEIFA 7 and 8) experienced the highest rates of every outcome, compared with every other SEIFA category. Trends over time analyses of OHCA outcomes by SES is required to further elucidate our understanding.

Strengths and limitations

The major strength of this study is the population-based approach to calculate incidence (as opposed to previously reported proportions), which is essential to accurately identify groups at-risk of OHCA and predictors of outcome (both of these are important to inform preventive strategies to improve public health).

Data linkage allowed analyses of remoteness and SES, by capturing residential postcode recorded within the hospital records. Due to the lack of bystander knowledge and the short window paramedics to collect information, residential postcode is often missing in pre-hospital data. The methods employed in this study hence overcome some usual limitations of pre-hospital research. Notably, the case identifying dataset (QAS OHCA Registry) has rigorous collection and reconciliation processes[23] to address some potential weaknesses of routine ambulance data collections, so there was close to 100% case capture.

The results of this study should be interpreted in the context of limitations. First, there are potential confounding factors that were not addressed, such as bystander interventions, initial rhythm, time to resuscitation and witnessed status. Second, there are likely limitations of the datasets used, such as coding intricacies (varying coders and coding practices over time) and level of completeness (although for the variables investigated this is likely to be very low). Third, SEIFA is a broad measure of SES, which is applied by region, rather than individually to a person. Last, there are small numbers in some sub-groups. This is of particular concern for younger aged adults (18–34 years), OHCA resulting in Unsustained-ROSC and people living in remote/very remote areas. Consequently, some 95% CIs were broad and included 1.0 for some associations, likely due to small numbers (type 2 error). In addition, these small numbers in some sub-groups inhibited a one-model approach to calculations with adjustments.

Conclusion

Since there is an increased risk of OHCA with increasing remoteness, rural-specific strategies should be continued and preferably further developed. These results also highlight that OHCA rates are higher in those exposed to socio-economic disadvantage, and this group experience less preferred outcomes. Prevention and management strategies for OHCA targeting lower socio-economic groups require focus. Over the 13 year period of this study, annual incidence of OHCA was significantly greater in males than females and incrementally increased with age, for each outcome.

Trends over time analyses of OHCA prevalence and outcome by age, gender, remoteness and SES are essential to build on the findings of this study and inform evaluation of the success of implemented strategies and the development of new ones.

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Competing interests

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Table S1. Annual age-standardised incidence rates by remoteness and socio-economic status and pre-hospital outcome in Queensland, Australia (per 100 000).

Supplemental Table 1: Annual age-standardised incidence rates by remoteness and socio-economic status and pre-hospital outcome in Queensland, Australia (per 100 000)

	No-Resus			No-ROSC			Unsustained-ROSC			Sustained-ROSC			Total events		
	Female	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*
Geographical Remoteness (ARIA)[1]															
Major Cities	25.15	47.79	35.50	14.21	39.41	25.75	1.05	2.54	1.73	5.73	13.71	9.46	46.14	103.46	72.45
Inner Regional	25.76	54.69	39.51	14.60	38.96	26.22	1.10	2.13	1.57	5.35	12.36	8.77	46.81	108.14	76.07
Outer Regional	27.96	61.31	44.44	17.51	42.40	29.72	0.78	2.45	1.61	5.95	11.99	8.93	52.21	118.15	84.70
Remote	29.32	63.07	47.42	13.22	26.58	20.59	0.41	1.36	0.80	4.30	7.95	6.35	47.25	98.96	75.16
Very Remote	34.02	79.08	58.11	25.03	44.98	35.29	1.32	2.37	1.85	3.87	11.48	7.71	64.23	137.91	102.96
Socio-economic status (SEIFA)[2]															
1&2	23.49	52.56	37.28	12.73	36.85	24.13	0.85	2.16	1.46	4.90	11.59	8.13	41.97	103.17	71.01
3&4	22.18	44.97	33.04	13.17	33.61	22.80	0.87	1.98	1.40	5.05	9.84	7.36	41.27	90.40	64.61
5&6	21.59	45.25	32.53	12.44	32.75	22.01	0.76	1.88	1.29	4.76	11.77	8.10	39.55	91.65	63.92
7&8	37.17	70.10	52.56	21.66	59.48	39.18	1.76	3.77	2.68	7.99	19.64	13.54	68.58	152.99	107.97
9&10	25.97	48.13	35.95	15.45	37.71	25.64	0.92	2.46	1.61	6.05	12.87	9.20	48.39	101.16	72.40

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [1]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [2]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was used to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [3]. Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage

4.3 Chapter Summary

- OHCA outcomes are usually reported as proportions of the OHCA population. This is the first study to report incidence of OHCA by pre-hospital outcome in Australasia.
- The annual crude incidence rate of total OHCA events was 73.95 (95%CI: 73.12-74.78) per 100,000 per annum. Rates were typically twice as high in males as they were in females for total events (males: 98.14 (95%CI: 96.78-99.49); females:50.32 (95%CI: 49.36-51.28)) and each outcome. Age-specific rates mostly showed the same pattern. This effect was more pronounced in age-standardised rates.
- Incidence of OHCA (per 100,000 per annum) increased incrementally with age (18-24 years: 0.59 per 100,000 per annum; 85+years:- 660.97 per 100,000 per annum). This pattern generally repeated for every outcome in both females and males.
- There was a higher rate of total OHCA events, and events resulting in No-Resus or No-ROSC for inner regional, outer regional and very remote areas (vs major cities), and reduced rates of Sustained-ROSC in outer regional, remote and very remote areas.
- The lowest rates of total events and every outcome (other than No-Resus) were observed in remote areas.
- There was an inverse association between total OHCA events and socio-economics status.
- People in areas categorised as high (but not the highest) advantage (SEIFA 7&8) experienced the highest rates of every outcome, compared with every other SEIFA category

4.4 Final Word (Chapter 4)

This study reports population-based incidence of pre-hospital outcomes of adult OHCA of cardiac aetiology in Queensland, Australia by age, gender, geographical remoteness and socio-economics status, so is an informative and novel addition to the literature. The broad time frame of this study (2002-2014) makes it ideal for trends over time analyses. These trends are essential to build on the findings of this study, as they can be used to inform evaluation of implemented strategies and the development of new ones. This is addressed in the following Chapter, in which temporal trends (2002-2014) of pre-hospital outcomes of adult OHCA of cardiac aetiology (Chapter 5; Publication 4) are investigated.

Chapter 5: Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002-2014): Trends over time

5.1 Overview

This Chapter is the second in a series of two publications exploring the epidemiology of pre-hospital outcomes of adult OHCA of presumed cardiac aetiology, attended by QAS paramedics in Queensland. It is the second Chapter addressing aim 2 *(To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia)* of the thesis (fourth publication) and focuses on temporal trends in population-based incidence overall and by pre-hospital outcome. Temporal trends have also been analysed by age, gender, geographical remoteness and socio-economic status. This study builds on the findings presented in the previous Chapter of this thesis (Chapter 4; Publication 3).

At the time this study was conceptualised, there were no studies reporting temporal trends in OHCA incidence by pre-hospital outcome. Therefore, this study provides a novel and important addition to the literature and facilitates evaluation of previously implemented strategies and the development of future ones.

As with the previous Chapter, all cases of adult OHCA of presumed cardiac aetiology in residents of Queensland attended by QAS paramedics in Queensland are included in this study (N=30,560). There are four mutually exclusive pre-hospital outcomes. These are the same as those described in the previous study (Chapter 4; Publication 3):

- No resuscitation (No-Resus): This group received no resuscitation attempt by QAS paramedics. This is the least preferred outcome
- No return of spontaneous circulation (No-ROSC): This group received a resuscitation attempt by QAS paramedics, but pre-hospital ROSC was not achieved at any stage
- ROSC not sustained to hospital (Unsustained-ROSC): This group received a resuscitation attempt by QAS paramedics, pre-hospital ROSC was achieved but it was not sustained to hospital
- ROSC sustained to hospital (Sustained-ROSC): This group received a resuscitation attempt by QAS paramedics, pre-hospital ROSC was achieved and it was sustained to hospital. This is the most preferred outcome

Figure A shows the position of this Chapter in the thesis.

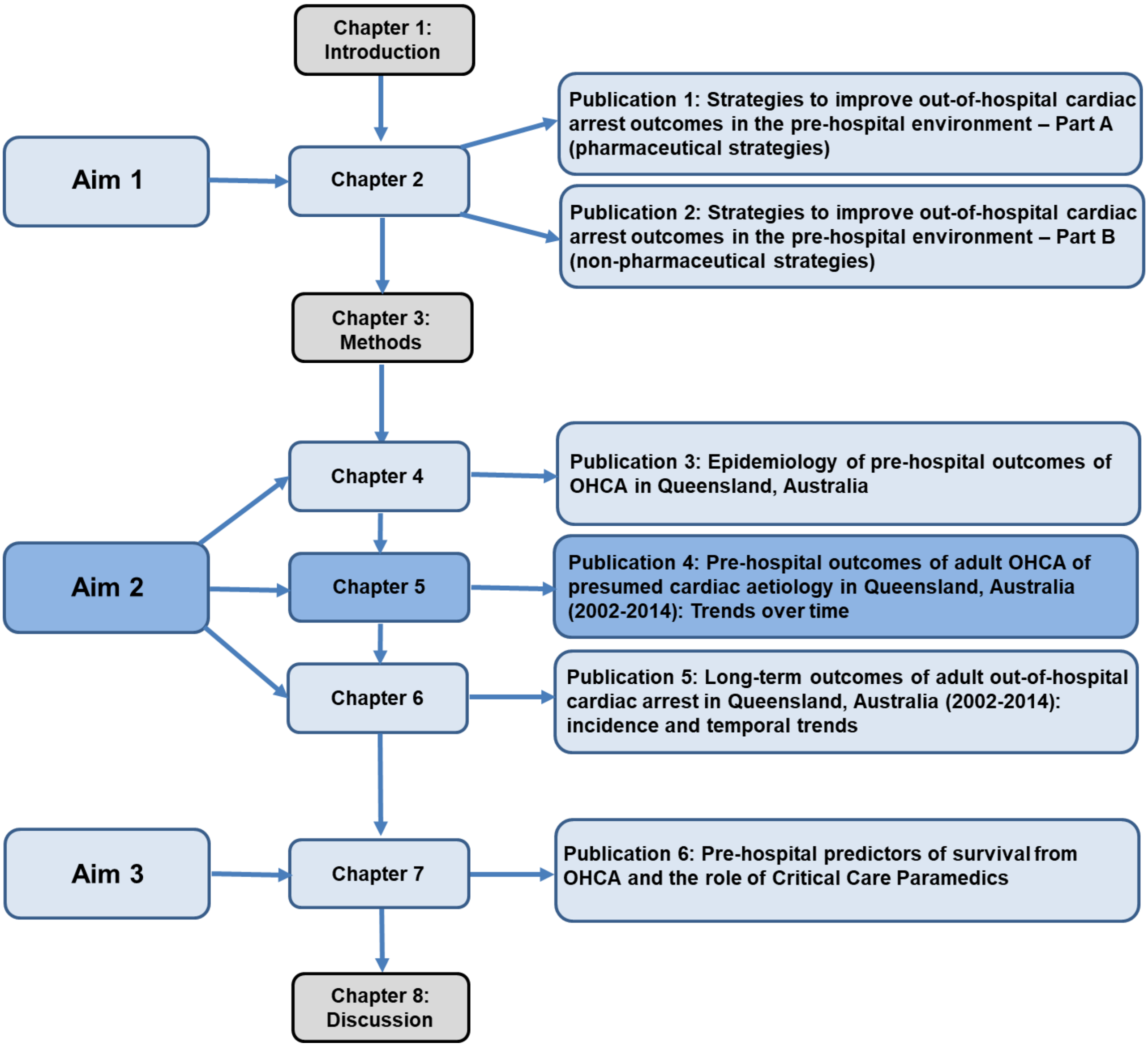

Figure A: Conceptual model of thesis – Aim 2, Chapter 5, Publication 4

5.2 Manuscript

This Chapter comprises the following manuscript that has been published in a peer-reviewed journal, and is inserted as a published PDF in the format required by the journal:

Pemberton K, Bosley E, Franklin RC and Watt K. Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002–2014): Trends over time. *Emergency Medicine Australasia*. 2019; **31**: 813-20.

Emergency Medicine Australasia (2019) doi: 10.1111/1742-6723.13353

ORIGINAL RESEARCH

Pre-hospital outcomes of adult out-of-hospital cardiac arrest of presumed cardiac aetiology in Queensland, Australia (2002–2014): Trends over time

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Abstract

Objective: To describe temporal trends in incidence of pre-hospital outcomes from adult out-of-hospital cardiac arrest (OHCA) of presumed cardiac aetiology attended by Queensland Ambulance Service (QAS) paramedics between 2002 and 2014, by age, gender, geographical remoteness and socio-economic status.

Methods: Cases included in this retrospective cohort study were identified from the QAS OHCA Registry. Included cases were linked with Queensland Hospital Admitted Patient Data Collection and Queensland Death Registry. Population data were obtained from the Australian Bureau of Statistics to calculate incidence rates for each year. Analyses were undertaken by four mutually exclusive pre-hospital outcomes: (i) no resuscitation (No-Resus); (ii) resuscitation, no pre-hospital return of spontaneous circulation (No-ROSC); (iii) resuscitation, pre-hospital return of spontaneous circulation not sustained to hospital (Unsustained-ROSC); and (iv) resuscitation, pre-hospital return of spontaneous circulation sustained to hospital (Sustained-ROSC). Trends over time were analysed for crude and specific rates for total OHCA events and for each outcome.

Results: Between 2002 and 2014, there were 30 560 OHCA cases. Crude incidence significantly increased over time for No-Resus and Sustained-ROSC, and significantly decreased for No-ROSC. These trends were reflected in major cities, inner and outer regional areas. There was a significant increase in Sustained-ROSC in remote areas, and no significant trends in very remote areas.

Conclusion: Incidence of withholding resuscitation and ROSC sustained to hospital have independently increased over time. Factors of middle age, more rural location and lower socio-economic status should all be targeted in the development and implementation of future strategies.

Key words: *cardiac arrest, emergency medical services, epidemiology, pre-hospital.*

Key findings

- Incidence of No-Resus and Sustained-ROSC significantly increased over time.
- Evidence of a positive impact of remote-specific strategies.
- Trends over time varied by SES – Sustained-ROSC increased over time for all categories.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality. Incidence differs globally[1,2] and changes over time, depending on the sub-group of interest.[3,4] Patient outcomes from OHCA are routinely reported as proportions;[2,5–9] however, incidence provides a more meaningful measure as it accounts for changes in population size and demography, better informing the true burden. Therefore, reporting incidence of outcomes from OHCA over time is preferable and essential to inform the impact of previous change and future direction. While there are published studies of temporal trends in OHCA incidence, there are none reporting temporal trends in OHCA incidence by outcome.

Several studies investigated OHCA incidence over time in the subgroup of patients who were in a shockable rhythm and received a resuscitation attempt;[10–12] all showed declining rates.

Two studies examined trends over time in OHCA incidence of patients who received a resuscitation attempt, by initial rhythm.[13,14] The first study (1992–2002) reported a reduction in shockable cases, increase in asystolic cases and no changes in cases of pulseless electrical activity (PEA).[13] The second study (2003–2012) reported increases in annual overall incidence, and by presenting rhythm (ventricular fibrillation/ventricular tachycardia and PEA/asystole), in

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males and females. Both of these studies also examined patient outcome (survival to admission and discharge; and in-hospital mortality, respectively), but by proportion of the initial population only, not incidence.

Two Australian studies, one in Western Australia (1997–2010)[4] and one in Queensland (2002–2014)[3] reported temporal trends in age- and gender-specific incidence rates for OHCA as well as age-standardised rates; decreases in age-standardised incidence were observed in both studies. An increase in incidence in the 50–64 years age group, largely attributable to females, was observed in the Queensland study.[3]

One Canadian study[15] investigated incidence from 2002 to 2012 in OHCA patients who had not died on ED arrival. Age- and gender-standardised, and gender-specific incidence did not change over time, but some changes were reported in age-specific rates (28% relative increase in 20–49 years and a 10% relative decrease in 85+ years). There were also improvements in 30 day and 1 year survival; however, this was by proportion only, not incidence.

In a study of 27 European countries, incidence rates of OHCA by outcome were reported[16] by country for resuscitation attempts (range 19–104), return of spontaneous circulation (ROSC) (range 6–32), survival (range 0.2–17.3) and survival in bystander witnessed events of suspected cardiac aetiology with an initial shockable rhythm (range 0.1–6.3), but not trends over time.

The prevalence and prognosis of medical conditions, particularly those of a time critical nature such as OHCA, are impacted by geographical remoteness and socioeconomic status (SES).[17] Age- and gender-specific rates stratified by geographic remoteness and SES, as well as age-standardised rates, have previously been reported by the authors for total OHCA events and by outcome.[18] However, temporal trends were not examined.

The aim of the present study is therefore to identify trends over time in pre-hospital outcomes of adult OHCA of presumed cardiac aetiology attended by Queensland Ambulance Service (QAS) paramedics between 2002 and 2014, by age, gender, geographic remoteness and SES. This provides a unique and informative addition to the epidemiological evidence base.

Methods

This retrospective cohort study involved linking three large data sources: (i) QAS OHCA Registry; (ii) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and (iii) Queensland Registrar General Death Registry. The inclusion/exclusion criteria and methods used for linkage processes and data collation have been previously reported.[18] Outcomes were: (i) no resuscitation (No-Resus); (ii) resuscitation, no pre-hospital ROSC (No-ROSC); (iii) resuscitation, pre-hospital ROSC not sustained to hospital (Unsustained-ROSC); and (iv) resuscitation, pre-hospital ROSC sustained to hospital (Sustained-ROSC). These outcomes differentiate between predictors of favourable longer-term outcomes.[19] Geographical remoteness (via Accessibility/Remoteness Index of Australia [ARIA])[20,21] and SES (via Socio-Economic Indexes for Areas [SEIFA], specifically Index of Relative Socio-Economic Advantage and Disadvantage)[22] were determined via residential postcode. Population data were obtained from the Australian Bureau of Statistics (see previous description for more detail).[18]

Analyses

Analyses were undertaken using STATA (15.1; StataCorp, College Station, TX, USA). Incidence rates for each outcome and total OHCA events were calculated for every calendar year then stratified by age-group, gender, geographical remoteness and SES. Age-standardised rates (directly standardised to Australian population 2001) were also calculated. Temporal trends in incidence rates were analysed using Poisson regression unless over dispersion was indicated by a goodness of fit, when negative binomial distribution regression was used.[23]

Ethics approval

Ethical approval for this study was obtained from Prince Charles Hospital Human Research Ethics Committee (approval number 15/QPCH/265), and from James Cook University Human Research Ethics Committee (approval number H5752). Access to confidential data was obtained via the Public Health Act through Queensland Health (approval number RD006708) and QAS Commissioner approval was obtained.

Results

Between 2002 and 2014, there were 30 560 eligible cases; 30 536 cases were available for analysis related to geographical remoteness (missing = 24) and 30 514 cases for analysis involving SES (missing = 46).[18] Crude and adjusted annual incidence rates by outcome, gender and age are presented elsewhere.[18]

Incidence of total OHCA events increased significantly between 2002 and 2014 (64.75–76.10 per 100 000; $P < 0.001$) (Fig. 1). Rates of total events significantly increased over time in males (85.79–99.71; $P < 0.001$) and females (44.25–53.09; $P < 0.001$). Rates of total OHCA events decreased in those aged 25–44 years and 65–84 years, but increased among those aged 45–64 years (45–54 years: 31.24–44.62 and 55–64 years: 79.54–97.43; $P < 0.001$) and in those aged 85+ years (554.86–688.52; $P = 0.007$) (Table 1).

Crude incidence of No-Resus and Sustained-ROSC increased significantly from 2002 to 2014 (27.66–40.17 and 6.31–9.99 per 100 000 respectively; $P < 0.001$); No-ROSC decreased significantly (28.76–24.02; $P < 0.001$); and Unsustained-ROSC did not change (Fig. 1, Table 1). Similar trends were observed when analyses were adjusted for age and gender; ARIA and gender; and SEIFA and gender (not shown). Similar results were also observed in gender-specific rates, except events resulting in Unsustained-ROSC in males, which significantly decreased during the study period ($P = 0.045$).

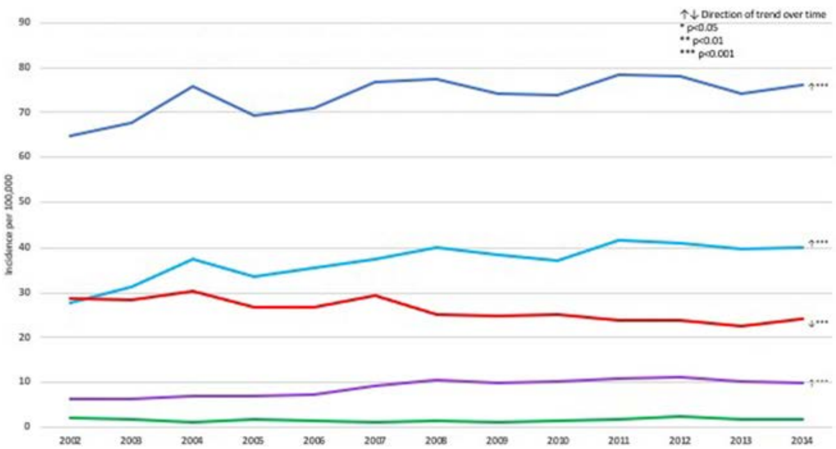

Figure 1. *Crude incidence of adult (18+ years) out-of-hospital cardiac arrest of cardiac aetiology by pre-hospital outcome, over time. (——), Total events; (——), No-Resus; (——), No-ROSC; (——), Unsustained-ROSC; (——), Sustained-ROSC.*

Incidence of events resulting in Sustained-ROSC increased in all age groups except those aged 25–34 years or 65–74 years (no consistent trends observed). Rates of events resulting in No-ROSC decreased in all age groups except those aged 85+ years (no trends). Events resulting in No-Resus increased in most age groups except 18–24 (no trend), 35–44, or 75–84 years.

There were 676 cases in the Unsustained-ROSC category. The only significant trends observed for this outcome were a decrease in rates in males, and an increase in males in major cities. No further description or interpretation was undertaken on this outcome measure.

Age/gender

Incidence of No-Resus (per 100 000 persons) increased ($P < 0.001$) over time for females (4.01–10.43) and males (17.21–30.43) aged 45–54 years and 55–64 years (14.08–24.53, $P = 0.002$; 48.45–72.55, $P < 0.001$), and also in males (but not females) aged 65–74 years (92.23–117.07, $P = 0.045$) and females (but not males) aged 85+ years (252.12–359.71, $P = 0.019$). No changes were observed in the 75–84 years age group for males or females. Rates among those aged 18–44 years either decreased or stayed the same (Table 1).

For OHCA resulting in No-ROSC, age- and gender-specific trends mostly reflected the crude rates (Fig. 1) – that is, rates decreased over time. Exceptions were among those aged 18–24 years (males and females), females aged 45–64 years and those aged 85+ years (males and females), where there were no consistent trends.

For OHCA resulting in Sustained-ROSC, rates significantly increased over time in both females and males aged 18–24 years (0.00–0.43; $P = 0.032$), 35–64 years (35–44 years: 1.64–2.46, $P = 0.046$; 45–54 years: 3.40–8.96, $P < 0.001$; and 55–64 years: 7.98–16.30, $P < 0.001$) and 75+ years (75–84 years: 32.17–41.75, $P = 0.017$; and 85+ years: 48.06–54.22, $P = 0.004$), with some exceptions. These were both females and males (independently) aged 18–24 and 75–84 years, and females aged 35–44 and 85+ years, where rates increased but not significantly. There were no significant changes over time in those 25–34 or 65–74 years.

Geographical remoteness (ARIA)

Incidence of total OHCA events increased significantly over time in every remoteness category, except very remote areas, where rates fluctuated markedly over the study period (most likely because of the smaller population in this category) (Fig. 2). The most profound increase was observed among people living in remote areas (incidence increased from 32.90 to 75.28 per 100 000). Incidence of OHCA resulting in No-Resus increased in major cities (25.76–39.37), inner regional (40.46–46.72) and outer regional areas (26.68–43.35) ($P < 0.001$, respectively); no trends were observed in remote or very remote areas. Events resulting in Sustained-ROSC increased significantly in all regions, except very remote areas, where no trends were observed. A significant increase over time in Sustained-ROSC was the only trend observed in remote areas (0–15.44; $P < 0.001$). No significant trends were observed in any of the outcomes in very remote areas. Incidence of OHCA events resulting in No-ROSC decreased significantly within major cities (29.16–22.59; $P < 0.001$), and among males (but not females) in inner regional (46.04–42.54; $P = 0.009$) and outer regional areas (41.30–35.54; $P = 0.010$) (Fig. 2, Table 1). After adjusting for remoteness and gender, there were significant increases in OHCA incidence resulting in No-Resus ($P < 0.001$) and Sustained-ROSC ($P < 0.001$), but significant decreases in OHCA resulting in No-ROSC ($P < 0.001$).

Socio-economic status (SEIFA)

Incidence of total OHCA events increased in areas categorised as lower relative advantage (Fig. 3, Table 1). The effect was strongest in the area defined as lowest relative advantage (SEIFA 1 and 2; increased from 67.05 to 83.96). No trends were observed in areas of higher advantage. The same pattern was observed for events resulting in No-Resus and Sustained-ROSC. Rates of events resulting in Sustained-ROSC also increased over time in areas defined as higher relative advantage (SEIFA 7 and 8: 8.73–13.26; $P < 0.001$), and for males but not females living in areas defined as the highest relative advantage (SEIFA 9 and 10: 4.92–11.84; $P = 0.010$). Rates of OHCA events resulting in

TABLE 1. *Trends over time (2002–2014) in crude and specific rates of out-of-hospital cardiac arrest by pre-hospital outcome, gender, age, remoteness and socio-economic status in Queensland, Australia*

	No-Resus			No-ROSC			Sustained-ROSC			Total events		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Crude	↑***	↑***	↑***	↓**	↓***	↓***	↑***	↑***	↑***	↑***	↑***	↑***
Age group (years)												
18–24	NS	NS	NS	NS	NS	↓*	NS	NS	↑*	NS	NS	NS
25–34	NS	↓**	↓**	↓*	↓***	↓***	NS	NS	NS	↓***	NS	↓***
35–44	↓***	NS	NS	↓***	↓**	↓***	NS	↑*	↑*	↓***	NS	↓*
45–54	↑***	↑***	↑***	NS	↓**	↓*	↑**	↑***	↑***	↑***	↑**	↑***
55–64	↑**	↑***	↑***	NS	↓***	↓***	↑***	↑***	↑***	↑***	↑**	↑***
65–74	NS	↑*	↑*	↓**	↓***	↓***	NS	NS	NS	NS	↓*	↓*
75–84	NS	NS	NS	↓***	↓***	↓***	NS	NS	↑***	NS	↓**	↓*
85+	↑*	NS	↑**	NS	NS	NS	NS	↑**	↑**	NS	NS	↑**
Geographical remoteness (ARIA)†												
Major cities	↑***	↑***	↑***	↓***	↓***	↓***	↑**	↑***	↑***	↑**	↑**	↑***
Inner regional	↑*	↑**	↑***	NS	↓**	↓**	↑***	↑***	↑***	↑**	↑**	↑**
Outer regional	↑*	↑***	↑***	NS	↓*	↓*	↑*	↑*	↑**	↑*	↑***	↑***
Remote	NS	NS	NS	NS	NS	NS	↑**	↑*	↑***	NS	↑**	↑**
Very remote	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Socio-economic status (SEIFA)‡												
1 and 2	↑**	↑***	↑***	NS	↓*	NS	↑***	↑***	↑**	↑**	↑**	↑***
3 and 4	↑***	↑***	↑***	NS	↓**	↓**	↑*	↑**	↑***	↑**	↑*	↑***
5 and 6	↑**	↑***	↑***	NS	↓***	↓***	↑***	↑***	↑***	↑**	↑*	↑***
7 and 8	NS	↑***	↑***	↓*	↓***	↓***	↑*	↑***	↑***	NS	NS	NS
9 and 10	NS	NS	NS	↓**	↓**	↓***	NS	↑*	↑**	NS	NS	NS

Trend over time indicated by ↑↓ or NS (no significant trend), as follows: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. †Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA).[20] Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories:[21] major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+. ‡SEIFA (Socio-Economic Indexes for Areas) was used to estimate socio-economic status in this study – specifically, the Index of Relative Socio-Economic Advantage and Disadvantage.[22] Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage. No-Resus, no resuscitation; No-ROSC, resuscitation, no pre-hospital ROSC; Sustained-ROSC, resuscitation, pre-hospital ROSC sustained to hospital.

No-Resus increased for males (but not females) in SEIFA category 7 and 8 (45.49–66.46; $P < 0.001$). For OHCA resulting in No-ROSC, rates decreased in areas categorised as low advantage (SEIFA 1 and 2: 40.74–37.72, $P = 0.027$; SEIFA 3 and 4: 41.97–31.33, $P = 0.003$) and middle advantage (SEIFA 5 and 6: 34.26–28.53; $P < 0.001$) for males, but not females. Rates decreased for both females and males living in areas of higher advantage (SEIFA 7 and 8: 38.43–31.62; SEIFA 9 and 10: 25.16–20.19; $P < 0.001$) (Fig. 3, Table 1). After adjusting for SES and gender, there were significant increases in OHCA resulting in No-Resus ($P < 0.001$) and Sustained-ROSC ($P < 0.001$), but significant decreases in OHCA resulting in No-ROSC ($P < 0.001$).

Discussion

This study investigated temporal trends in incidence of pre-hospital outcomes of adult OHCA over a 13 year period, by age, gender, remoteness

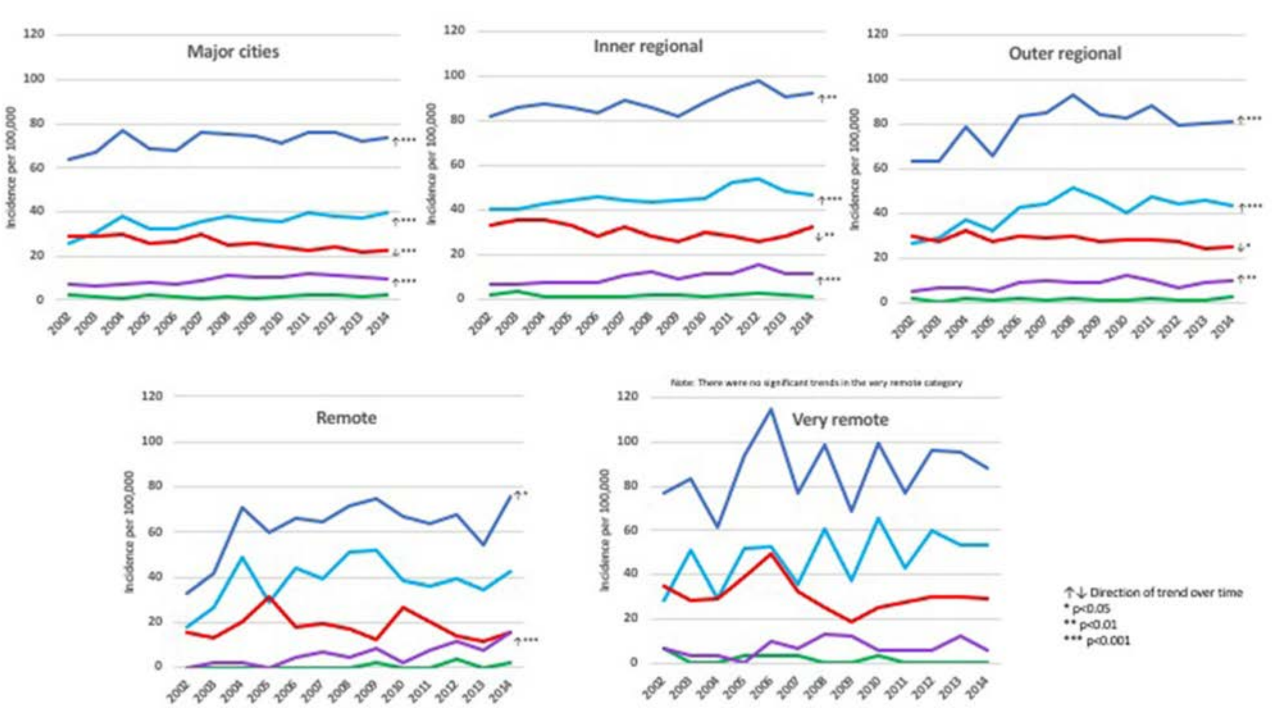

Figure 2. *Incidence of adult (20+ years) out-of-hospital cardiac arrest of cardiac aetiology by pre-hospital outcome and geographical remoteness.* Note*: population data was not available for analyses involving ARIA and SEIFA for adults aged <20 years. (——), Total events; (——), No-Resus; (——), No-ROSC; (——), Unsustained-ROSC; (——), Sustained-ROSC.*

and SES. It is an extension of a recent study[18] and is the first investigation known to the authors where trends in incidence of OHCA have been reported at this level of detail (by outcome, age and gender, remoteness and SES).

Incidence rates for each outcome and total OHCA events were calculated for every calendar year then stratified by age-group, gender, geographical remoteness and SES.

The increase over time in incidence of OHCA events overall was largely attributable to the middle-age years in this study. This is likely a reflection of the higher exposure to risk factors of chronic disease in the middle-age years and the resultant recent chronic disease epidemic.[24] An increase in incidence over time in OHCA resulting in No-Resus (in crude and adjusted rates) was observed. A possible explanation is an increasingly stringent application of resuscitation attempts, resulting in the growing exclusion of those less survivable, but not futile. However, if this was the case it would be expected that the rate of No-Resus would increase, with decreases across the other three outcome groups (No-ROSC, Unsustained-ROSC, and Sustained-ROSC), reflecting the shift from resuscitation attempts to withholding resuscitation. While there was a significant decrease observed in the No-ROSC, a significant increase was observed in the Sustained-ROSC, and a small increase in Unsustained-ROSC (non-significant). In addition, the observed increases in No-Resus have not been constant, mostly occurring prior to the implementation of new resuscitation guidelines in 2008. Since 2008, the No-Resus rate has remained consistent while Sustained-ROSC has continued to increase. Finally, resuscitation rates in QAS are consistent with those of other Australian and New Zealand services.[25] Over the period of this study, paramedic education levels have improved and training methods have become more sophisticated. In addition, training and guidelines have increased focus on patient-specific decision-making.[26] A decision to commence resuscitation now includes multiple factors such as co-morbidities and the patient's expected clinical course, whereas previously, decisions were protocol-driven with broad general criteria and little flexibility. Hence, we would now expect paramedics to attempt resuscitation less often. When this finding is considered in conjunction with the reduction in incidence of OHCA resulting in No-ROSC (in crude and adjusted rates), this can be interpreted as evidence that decisions not to resuscitate are being applied appropriately; with increasing patient focus, while adhering to current guidelines.[27]

Previous studies have focused on outcomes as proportions among OHCA cases only. This study is a population-based study that adjusts for age and gender and thus provides a more robust measure of incidence at a population level. Therefore, the significant increase over time in incidence of OHCA resulting in Sustained-ROSC (the most positive OHCA outcome in this study) in crude and adjusted rates is a reassuring finding of improving care. This level of certainty on improving outcomes at a population level has not been previously ascertained, so is a unique and positive finding.

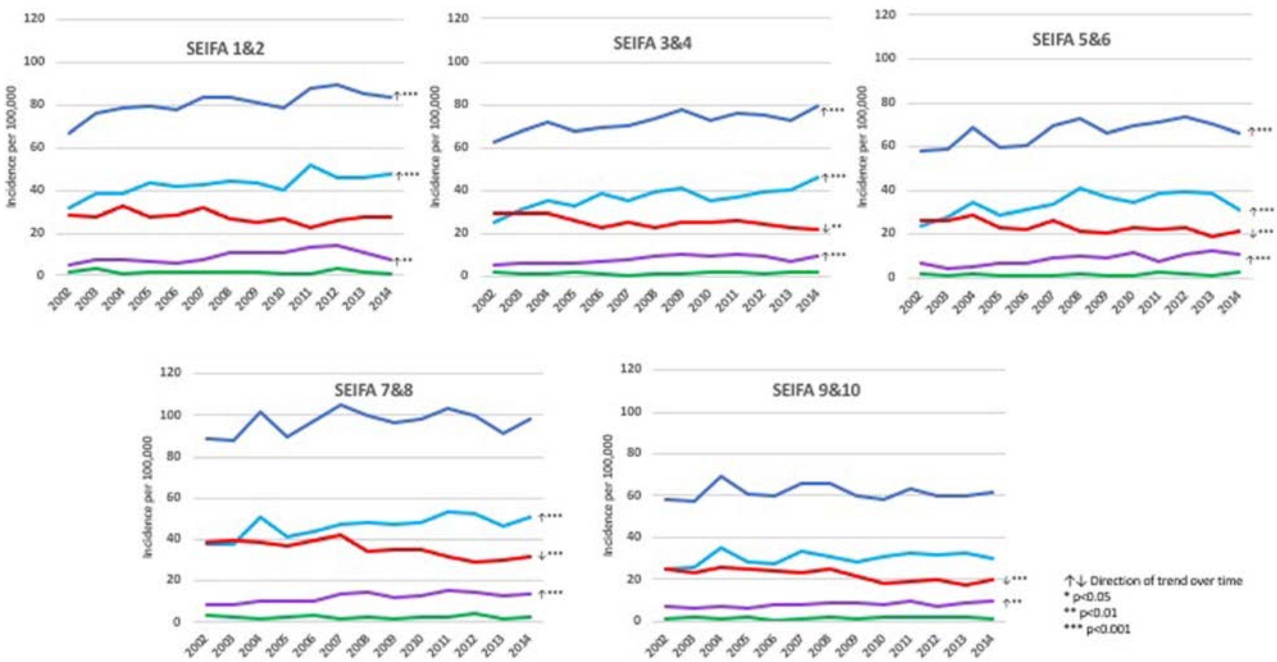

Figure 3. *Incidence of adult (20+ years) out-of-hospital cardiac arrest of cardiac aetiology, by pre-hospital outcome and socio-economic status.* Note: *population data was not available for analyses involving ARIA and SEIFA for adults aged <20 years. (——), Total events; (——), No-Resus; (——), No-ROSC; (——), Unsustained-ROSC; (——), Sustained-ROSC.*

Increases in preferred outcomes over the time period of this study are likely the result of a number of factors. First, the evidence base of the OHCA field has grown substantially, resulting in changes in the 2005 and 2010 ILCOR recommendations[28–31] and Australian Resuscitation Council guidelines – all adopted by QAS. These included a change in compression to ventilation ratio in 2005 (from 15:2 to 30:2) and additional emphasis on high quality CPR and patient-specific care, to include addressing reversible causes. Second, the QAS developed a greater focus on improving OHCA outcomes, including development of the OHCA initiative.[32] Third, as mentioned previously, paramedic education has developed over the time of this study. These multiple changes all likely contribute to better quality patient-specific care, leading to positive outcomes.

Geographical remoteness and socio-economic status

The absence of changes over time in OHCA resulting in No-Resus in remote/very remote areas requires further investigation. It is likely that rates of No-Resus in remote/very remote areas have always been higher than in areas less rural, because of factors such as longer response times, hence, strategies to be more selective in commencing resuscitation did not impact as profoundly.

In this study, rates of Sustained-ROSC (the most preferred outcome) increased in all remoteness groups, except very remote. This positive finding suggests that the implemented remote-specific strategies, such as community engagement initiatives,[33,34] are worthwhile; as well as those non-specific to rurality. The lack of change in the very remote group suggests there is still work to be done, but this observation may be because of smaller numbers in these areas. Regardless, this is evidence of the positive impact of remote-specific strategies, so these should at least be maintained and preferably further developed.

In this study, trends over time varied by SES. Rates of OHCA resulting in No-ROSC decreased over time in most SEIFA categories, and rates of OHCA resulting in Sustained-ROSC increased over time for all categories. This may reflect more patient-focused decision-making regarding resuscitation, which is affected by several factors, including bystander CPR, time interval between collapse and calling ambulance and underlying health state (e.g. chronic disease; other risk factors for OHCA).

Strengths and limitations

Strengths and limitations of this retrospective cohort study have been reported previously.[18] A major strength was the population-based approach to calculate temporal trends of incidence by outcome – every OHCA of cardiac aetiology in adult residents of Queensland attended by QAS during the study period was included, therefore selection bias is not likely. Measurement bias was also not likely as routinely collected data were used. Nevertheless, this was an observational study and therefore the findings must be interpreted in the context of inherent biases. Causality cannot be assessed using this study design; however, this was not the focus of the present study. A further major strength is the linking of three large datasets to collate more accurate and complete information. Limitations include: confounding factors not accounted for; dataset accuracy, completeness and consistency at source; using residential postcode to estimate SES and geographical remoteness; and the likely presence of type 2 error in some calculations. The latter is most relevant as an explanation for the lack of trends noted in very remote areas, and for the outcome group Unsustained-ROSC, which restricts meaningful interpretation for these groups. The purpose of this paper was to examine temporal trends of pre-hospital outcomes. An important next step is to examine temporal trends of longer-term outcomes such as survival to 30 and 365 days.

Conclusion

Incidence of OHCA resulting in No-Resus and Sustained-ROSC has increased over time in Queensland. This could be evidence of improved selectiveness by paramedics in the application of resuscitation with fewer inappropriate resuscitation attempts and more preferred outcomes when resuscitation is attempted. These positive findings could potentially be interpreted as evidence of increased patient-specific care, because of a multitude of general and OHCA-specific changes in practice, but further exploration using a more robust study design is required. Increased incidence of total OHCA events is largely attributable to the middle-age years in this population-based Queensland study, and likely reflects the chronic disease epidemic. Future strategies should be developed and implemented accordingly.

There is some evidence that strategies implemented during the study period have redressed some of the healthcare issues of remoteness. This focus should be continued and developed. Lower socio-economic groups require attention.

Acknowledgements

We acknowledge and thank Dr Peter Aitken, Medical Director, Retrieval and counter disaster unit, all paramedics and staff involved with OHCA data collection and management at QAS, and the DLU at QH.

Competing interests

None declared.

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5.3 Additional Analyses

Temporal trends of incidence rates for total events and by outcome were calculated adjusting for age and gender, ARIA & gender and SEIFA & gender but were not reported in this publication due to publishing constraints. These are presented for interest in Table 2 below.

Table 2: Trends over time (2002-2014) in adjusted incidence rates, by pre-hospital outcome in Queensland, Australia

	No-Resus	No-ROSC	Sustained-ROSC	Total events
Age & gender adjusted	↑***	↓***	↑***	NS
ARIA[1] & gender adjusted	↑***	↓***	↑***	↑***
SEIFA[2] & gender adjusted	↑***	↓***	↑***	↑***

No-Resus = No resuscitation; No-ROSC = Resuscitation, no pre-hospital ROSC; Sustained-ROSC = Resuscitation, pre-hospital ROSC sustained to hospital

Trend over time indicated by ↑↓ or NS (no significant trend), as follows: * p<0.05; ** p<0.01; *** p<0.001

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was used to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage

5.4 Chapter Summary

- This is the first published study to report temporal trends in OHCA incidence by pre-hospital outcome.
- Incidence of total OHCA events increased significantly between 2002-2014 overall (64.75-76.10 per 100,000; $p<0.001$) and independently in both males (85.79-99.71; $p<0.001$) and females (44.25-53.09; $p<0.001$).
- Crude incidence of No-Resus and Sustained-ROSC increased significantly from 2002-2014 (27.66-40.17 and 6.31-9.99 per 100,000 respectively; $p<0.001$) while No-ROSC decreased significantly (28.76-24.02; $p<0.001$). This suggests an increase in appropriate selectiveness by paramedics when deciding to attempt resuscitation and increasing preferred outcomes when resuscitation is attempted. Rates of Unsustained-ROSC did not change over time. Similar trends were observed in most age-specific rates and when analyses were adjusted for age and gender; ARIA and gender; and SEIFA and gender.
- Events resulting in Sustained-ROSC increased significantly in all regions except very remote areas. No significant trends were observed in any of the outcomes in very remote areas.
- Incidence of total OHCA events increased in areas categorised as lower relative advantage (SEIFA 1&2; SEIFA 3&4; SEIFA 5&6). No trends were observed in areas of higher advantage (SEIFA 7&8; SEIFA 9&10).
- Rates of events resulting in Sustained-ROSC increased over time in all SES groups.

5.5 Final Word (Chapter 5)

This study investigates temporal trends of outcomes of adult OHCA of cardiac aetiology attended by QAS paramedics in Queensland. This study provides a novel and informative addition to the literature. Nevertheless, longer term survival from OHCA provides a more informative measure to the burden on public health. This is addressed in the following Chapter, in which the epidemiology and temporal trends of adult OHCA of cardiac aetiology by long term outcomes, including survival to 365 days+ (Chapter 6; Publication 5), are investigated.

Chapter 6: Long-term outcomes of adult out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): Incidence and temporal trends

6.1 Overview

This Chapter comprises the fifth publication in this thesis and explores the epidemiology and temporal trends of long-term outcomes of adult OHCA of presumed cardiac aetiology attended by QAS paramedics in Queensland. This is the third Chapter that addresses aim 2 *(To explore epidemiology and temporal trends (2002-2014)* of OHCA in Queensland, Australia) of the thesis.

To date, there are no studies in which temporal incidence of OHCA outcomes have been reported beyond ROSC sustained to hospital. Long term outcomes are better predictors of patients' ongoing health care needs, quality of life and burden on public health than pre-hospital outcomes, so this study fills an important gap in the evidence base. This study complements the work presented in Chapters 4 and 5 which included all cases of adult OHCA of presumed cardiac aetiology in residents of Queensland attended by QAS paramedics (N=30,560) and described incidence and temporal trends of four pre-hospital outcomes, as follows: No resuscitation; No ROSC; Unsustained ROSC; and sustained ROSC (Chapter 4, Publication 3 and Chapter 5, Publication 4).

All cases of adult OHCA of presumed cardiac aetiology in residents of Queensland attended by QAS paramedics in Queensland where survival to hospital admission was recorded (N=4393) are included in the research described in this Chapter (Chapter 6, Publication 5).

Three mutually exclusive outcomes were analysed:

- Survival to less than 30 days (Surv<30days): This group survived to hospital admission but died in 29 days or less post the OHCA event. This is the least preferred outcome
- Survival to 30-364 days (Surv30-364days): This group survived to 30-364 days post the OHCA event
- Survival to 365 days or more (Surv365days+): This group survived to 365 days or more post the OHCA event. This is the most preferred outcome

Figure A contextualises this Chapter in the thesis.

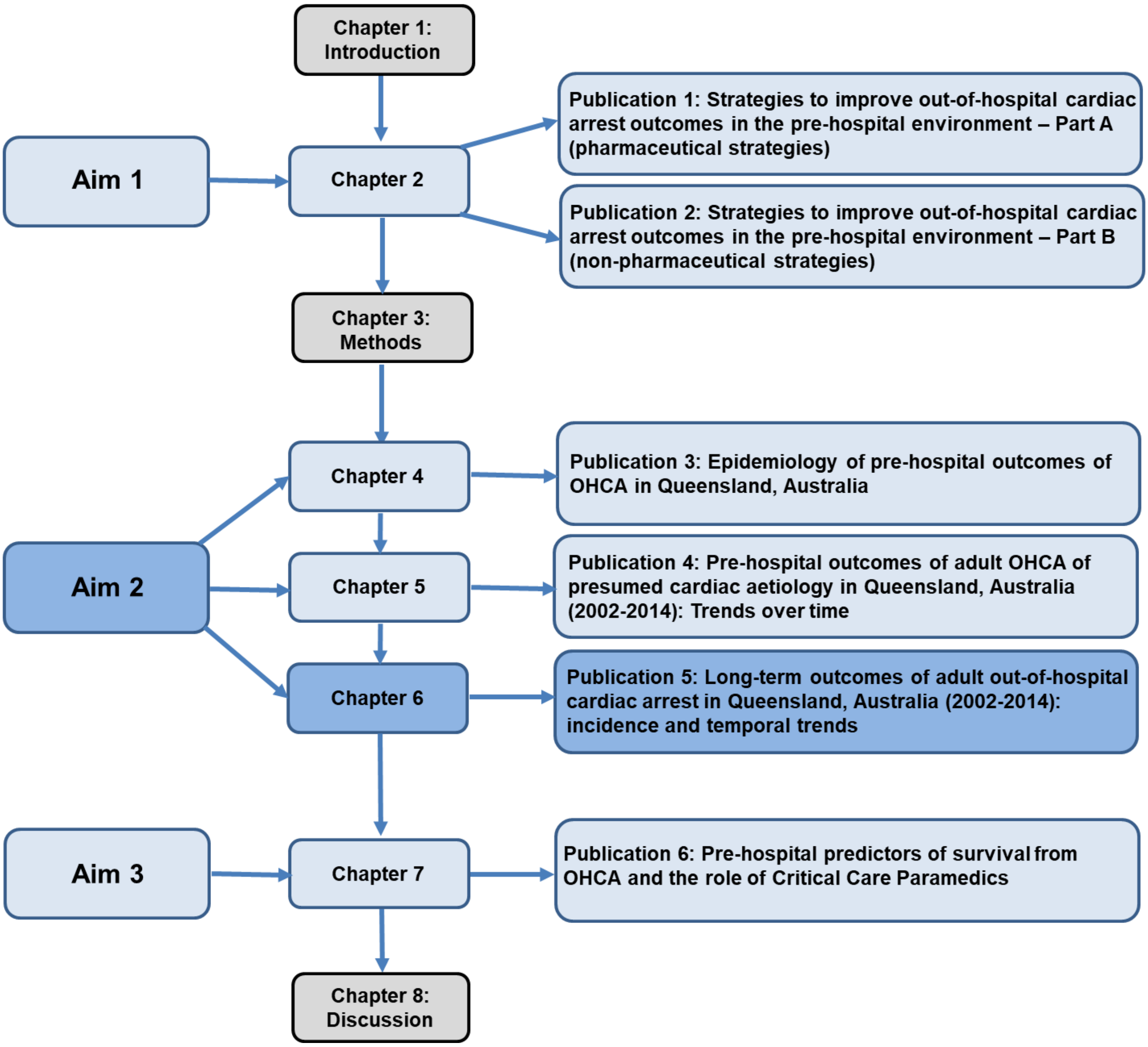

Figure A: Conceptual model of thesis – Aim 2, Chapter 6, Publication 5

6.2 Manuscript

This Chapter comprises the following manuscript that has been accepted for publication in Heart:

Pemberton K, Franklin RC, Bosley E and Watt K. Long-term outcomes of out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): incidence and temporal trends. *Heart. In press*. 2020.

This article is inserted in the format specified by Heart. Supplementary material supporting this article is presented prior to the Chapter summary.

Long-term outcomes of adult out-of-hospital cardiac arrest in Queensland, Australia (2002-2014): incidence and temporal trends

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Short Title: Long-term outcomes of adult OHCA in Queensland, Australia (2002-2014)

Paper word Count: 2971

Abstract word count: 245

Abstract:

Objective: To describe annual incidence and temporal trends (2002-2014) in incidence of long-term outcomes of adult out-of-hospital cardiac arrest (OHCA) of presumed cardiac aetiology attended by Queensland Ambulance Service (QAS) paramedics, by age, gender, geographical remoteness and socio-economic status (SES).

Methods: This is a retrospective cohort study. Cases were identified using the QAS OHCA Registry and were linked with entries in Queensland Hospital Admitted Patient Data Collection and Queensland Registrar General Death Registry. Population data were obtained from the Australian Bureau of Statistics to calculate incidence. Inclusion criteria were adult (18years+) residents of Queensland, who suffered OHCA of presumed cardiac aetiology and survived to hospital admission. Analyses were undertaken by three mutually exclusive outcomes: 1) Survival to less than 30 days (Surv<30days); 2) Survival from 30-364 days (Surv30-364days); and 3) Survival to 365 days or more (Surv365days+). Incidence rates were calculated for each year by gender, age, remoteness and SES. Temporal trends were analysed.

Results: Over the 13-years there were 4,393 cases for analyses. Incidence of total admitted events (9.72-10.13; $p<0.01$), Surv30-364days (0.18-0.42; $p<0.05$) and Surv365days+ (1.94-4.02; $p<0.001$) increased significantly over time, no trends were observed for Surv<30days. An increase in Surv365days+ over time was observed in all remoteness categories and most SES categories.

Conclusion: Evidence suggests that implemented strategies to improve outcomes from OHCA have been successful and penetrated groups living in more remote locations and the lower socio-economic groups. These populations still require focus. Ongoing reporting of long-term outcomes from OHCA should be undertaken using population-based incidence.

Key Questions

- What is already known about this subject?

Previous studies of OHCA have investigated trends over time in outcomes up to hospital arrival only, or where longer term outcomes have been measured, these are usually reported as proportions of the total OHCA population. Incidence is a measure of disease frequency that facilitates more meaningful comparisons within areas of the same country, between countries, and over time, where the population (and composition) changes. Hence, this is a more informative measure of OHCA and outcomes.

- What does this study add?

This is the first study known to the authors in which temporal incidence of OHCA outcomes of presumed cardiac aetiology have been reported beyond ROSC sustained to hospital (up to

365 day survival), by age, gender, geographical remoteness and socioeconomic status. Survival to 365 days or more has improved.

- How might this impact on clinical practice?

Long term outcomes are much better predictors of patients' ongoing health care needs, quality of life and burden on public health. Findings can usefully inform strategy evaluation and development in the prehospital/emergency sector and beyond.

INTRODUCTION:

Out of hospital cardiac arrest (OHCA) is an immediately life-threatening condition. Incidence of OHCA differs globally[1, 2], but in recent times survival rates have consistently been low worldwide.[1] Understanding patient outcomes from OHCA helps inform the burden of OHCA on public health, therefore, it is imperative to monitor incidence and outcomes.

Outcomes are usually reported as proportions of the total OHCA population, and often trends over time of these proportions are reported.[3-6] While these measures are useful to indicate the success of implemented strategies and the requirement and focus of future ones, incidence is an epidemiologically preferable measure of disease frequency that includes population size and a measure of time, which are more informative than the traditional measures of OHCA and outcomes reported in the literature, and facilitate more meaningful comparison of different areas within the same country, between countries, and over time (where there are likely to be population (and composition) changes).

Temporal trends in OHCA have been reported in several studies, but outcome has not. Decreases in age-standardised incidence over time were reported in two Australian studies, one in Western Australia[7] and one in Queensland[8]. Several studies have reported incidence of OHCA over time by rhythm, which although not an outcome, is a widely accepted indicator of outcome. In four of these studies, rates decreased over time in shockable patients only[9-12] and one study, rates in asystole increased but there were no observed changes in pulseless electrical activity patients.[11]

There are few papers that report incidence by outcome. The EuReCa ONE study reported one-month incidence (per 100,000 persons) of OHCA outcomes by country for resuscitation attempts (range 19-104), return of spontaneous circulation (ROSC) (range 6-32), survival (range 0.2-17.3) and survival in bystander witnessed events of suspected cardiac aetiology, with an initial shockable rhythm (range 0.1-6.3).[13] A Canadian study[14] investigated temporal trends (2002-2012) in incidence of OHCA patients who had not died upon ED arrival; changes were reported in some age-specific rates (28% relative increase in 20-49 years and a 10% relative decrease in 85 years+), but there were no changes in gender-specific or age/gender-standardised rates.

The authors have previously reported annual incidence of OHCA outcomes over a 13-year period in Queensland.[15] The outcomes were 1) No-Resus (37.31 per 100,000); 2) No-ROSC (25.98 per 100,000); 3) Unsustained-ROSC (1.64 per 100,000); and 4) Sustained-ROSC (9.03 per 100,000). Incidence of these outcomes were also reported by age, gender, geographical remoteness and socio-economic status (SES): incidence of OHCA increased with remoteness and socio-economic disadvantage, and less preferred outcomes were observed in those exposed to socio-economic disadvantage. Trends over time in these pre-hospital outcomes were reported separately, again stratified by age, gender geographical remoteness and SES.[16] Incidence of OHCA resulting in no resuscitation and sustained ROSC increased over time, suggesting improvements of increased selectiveness by paramedics in the application of resuscitation and more preferred outcomes when resuscitation is attempted.

To date, there are no studies in which temporal incidence of OHCA outcomes have been reported beyond ROSC sustained to hospital. However, long term outcomes are much better predictors of patients' ongoing health care needs, quality of life and burden on public health.[17]

The aim of this study is to fill this important gap in the evidence base and report incidence and identify trends over time of long-term outcomes (up to 365-day survival) of adult OHCA of presumed cardiac aetiology by age, gender, geographical remoteness and SES.

METHOD:

Queensland is a northern state of Australia and comprises 1.853 million km², with a population of approximately 5 million.[18] The Queensland Ambulance Service (QAS) have been described previously.[19] Australia has a universal health care system and in Queensland there is community ambulance cover (meaning that access is free to all residents of Queensland). Three data sources were linked in this retrospective cohort study of all OHCA events attended by QAS paramedics between 2002-2014, where survival to hospital admission occurred. These were: 1) QAS OHCA Registry; 2) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and 3) Queensland Registrar General (RG) Death Registry. The QAS OHCA Registry was used to identify cases, the method for which has been previously described.[15] The same selection criteria were used as in the two previously reported studies[15, 16] , except that in the present study, additional cases were excluded (post linkage) if linkage was unsuccessful (n=246) or the patient did not survive to admission (n=25921) (Supplement 1).

Specialised linkage software was used by the Data Linkage Unit (DLU) in Queensland Health to link the selected cases with QHAPDC and the RG Death Registry using deterministic and probabilistic methodologies, supplemented by clerical review. Data linkage allowed the collation of a more complete and accurate dataset for analysis by: 1) the provision of additional variables, including the long-term outcomes specifically required for this study; and 2) multiple sources of information for the same variable such as gender, age and residential postcode. Where contradictions occurred between datasets, the final decision relied firstly on the accuracy of the RG Death Registry data, followed by QHAPDC data, followed by QAS data.

Geographical remoteness (via ARIA Accessibility/Remoteness Index of Australia),[20, 21] was determined via residential postcode. Remoteness was categorised as: major cities, inner regional, outer regional, and remote/very remote (ARIA categories 4 and 5 were combined due to sample size). SEIFA was split into deciles, with higher deciles reflecting higher relative advantage), then categorised into 5 groups. Postcodes were also mapped to the Socioeconomic Index For Areas (SEIFA), and specifically the Index of Relative Socioeconomic Advantage and Disadvantage (ISRAD)[22] . IRSAD was created by the Australian Bureau of Statistics to measure the economic and social conditions of an area, and does not reflect individual-level socio-economic status.

Population data were obtained from the Australian Bureau of Statistics (ABS)[23] in order to calculate incidence rates, as previously described.[15] Population data by statistical local area 2 (SA2) and age group were used for analyses involving ARIA and SEIFA but were only available for adults 20years+. Hence, cases were excluded from any analyses involving ARIA and SEIFA if age <20yrs (Supplement 1) (see previous description for more detail).[15]

Three mutually exclusive outcomes were analysed. These were 1) survival to admission, but not to 30days (Surv<30days); 2) survival to 30-364days (Surv30-364days); and 3) survival to 365days or more (Surv365days+). These are routinely reported longer term outcomes from OHCA.[17]

Analyses

Analyses were undertaken using Microsoft Excel (16.12) and STATA (15.1). Incidence rates for each outcome and total OHCA events were calculated overall and for every calendar year by age-group and gender. Rates were then stratified by geographical remoteness and SES. Age-standardised rates (directly standardised to the Australian population 2001) were calculated for total OHCA events and each outcome for each calendar year and for the study period overall, then stratified by gender, remoteness, and SES. Relative risks (specifically, rate ratios) and 95% CIs were calculated to quantify risk factors for total OHCA events resulting in hospital admission, and by each of the three outcomes. For example, to quantify risk of survival to 365days+ in males relative to females, RR= incidence of survival to 365days+ in males / incidence of survival to 365days+ in females.

Poisson regression was used to analyse temporal trends in incidence rates unless over dispersion was indicated by a goodness of fit, when negative binomial distribution regression was used.[24]

Ethics approval

Ethical approval for this study was obtained from Prince Charles Hospital Human Research Ethics Committee (approval number 15/QPCH/265), and from James Cook University Human Research Ethics Committee (approval number H5752). Access to confidential data was obtained via the Public Health Act through Queensland Health (approval number RD006708).

Patient and public involvement

It was not appropriate or possible to involve patients or public in the design, conduct, reporting or dissemination plans of our research.

RESULTS:

Over the study period (2002-2014), there were 4393 cases of OHCA attended by QAS paramedics where survival to hospital admission was recorded (from hereon in, this group will be referred to as 'Total admitted events'). Four of these cases were excluded for analyses on remoteness (leaving 4389), and five for analyses on SES (leaving 4388). One of these excluded cases was <20 years, three cases had postcodes for which mapping to ARIA and SEIFA categories was not available and one case had a postcode for which mapping to a SEIFA category only was not available. These five cases were included in analyses not involving remoteness and/or SES. Only 246 cases were not linked to either QHAPDC or the RG Death Registry (likely due to administrative errors such as missing or inaccurate linkage variables, such as name and age), providing a linkage sensitivity rate of 99.2% (Supplement 1).

Crude rates

All incidence rates are expressed per 100,00 population per year. Crude incidence for total admitted events was 10.63 (95%CI: 10.32-10.95). For survival to admission but not to 30days, incidence was 7.05 (95%CI: 6.79-7.31), for survival to 30-364days incidence was 0.27 (95%CI: 0.22-0.32), and for survival to 365days+ it was 3.31 (95%CI: 3.13-3.48). Table 1 shows the annual crude rates for each outcome and for total admitted events, as well as age-, gender-specific incidence rates, and age-standardised rates. Crude incidence of total admitted events, survival to 30-364days and to 365days+ increased significantly over time, but no trends were observed for survival <30days (Figure 1). The same results were observed for gender-specific rates (Table 2), with exception of survival to 30-364days in males and total admitted events among females, where no trends were evident.

Table 1: Adult OHCA incidence rates (age-, gender-specific; and age-standardised) by long-term outcome in Queensland, Australia (per 100,000 population per year), 2002-2014

	Surv<30days n=2,913			**Surv30-364days n=113**			**Surv365days+ n=1,367**			**Total admitted events n=4,393**		
	Female *n=1,014*	*Male* *n=1,899*	*Total* *n=2,913*	*Female* *n=33*	*Male* *n=80*	*Total* *n=113*	*Female* *n=332*	*Male* *n=1,035*	*Total* *n=1,367*	*Female* *n=1,379*	*Male* *n=3,014*	*Total* *n=4,393*
18-24 **n=13**	0.11 (0.00-0.24)	0.22 (0.04-0.39)	0.17 (0.06-0.28)	0	0.04 (0.00-0.11)	0.02 (0.00-0.05)	0.04 (0.00-0.11)	0.07 (0.00-0.17)	0.06 (0.00-0.12)	0.15 (0.00-0.30)	0.33 (0.11-0.54)	0.24 (0.11-0.37)
25-34 **n=28**	0.05 (0.00-0.12)	0.18 (0.05-0.32)	0.12 (0.04-0.19)	0	0	0	0.16 (0.03-0.28)	0.34 (0.15-0.52)	0.25 (0.14-0.36)	0.21 (0.06-0.35)	0.52 (0.29-0.75)	0.36 (0.23-0.50)
35-44 **n=211**	0.48 (0.26-0.69)	2.20 (1.73-2.66)	1.33 (1.07-1.58)	0.03 (0.00-0.07)	0.05 (0.00-0.12)	0.04 (0.00-0.08)	0.40 (0.20-0.60)	2.22 (1.76-2.69)	1.30 (1.05-1.55)	0.90 (0.61-1.20)	4.47 (3.81-5.14)	2.67 (2.31-3.03)
45-54 **n=605**	2.14 (1.67-2.61)	5.90 (5.11-6.68)	4.00 (3.55-4.46)	0.08 (0.00-0.17)	0.35 (0.16-0.55)	0.22 (0.11-0.32)	1.39 (1.01-1.77)	6.52 (5.70-7.35)	3.94 (3.48-4.39)	3.61 (3.00-4.22)	12.77 (11.62-13.93)	8.15 (7.50-8.80)
55-64 **n=950**	5.58 (4.73-6.42)	13.01 (11.71-14.29)	9.32 (8.55-10.09)	0.13 (0.00-0.26)	0.49 (0.24-0.74)	0.31 (0.17-0.46)	2.37 (1.82-2.92)	9.81 (8.70-10.93)	6.12 (5.49-6.74)	8.08 (7.06-9.10)	23.31 (21.60-25.03)	15.75 (14.75-16.75)
65-74 **n=1,059**	12.37 (10.80-13.94)	24.78 (22.56-27.00)	18.58 (17.21-19.94)	0.52 (0.20-0.84)	0.83 (0.42-1.24)	0.68 (0.42-0.94)	4.37 (3.43-5.30)	12.16 (10.60-13.71)	8.26 (7.35-9.17)	17.25 (15.40-19.11)	37.77 (35.02-40.51)	27.51 (25.86-29.17)
75-84 **n=1,051**	25.03 (22.22-27.83)	51.22 (46.80-55.65)	36.83 (34.31-39.36)	0.74 (0.26-1.22)	1.99 (1.12-2.87)	1.30 (0.83-1.78)	5.40 (4.10-6.70)	13.55 (11.28-15.83)	9.07 (7.82-10.33)	31.16 (28.03-34.29)	66.77 (61.72-71.83)	47.21 (44.36-50.06)

Table 1, continued

	Surv<30days n=2,913			**Surv30-364days n=113**			**Surv365days+ n=1,367**			**Total admitted events n=4,393**		
85+ n=476	37.95 (32.68-43.22)	71.15 (61.21-81.08)	49.42 (44.56-54.29)	1.14 (0.23-2.06)	4.69 (2.14-7.25)	2.37 (1.31-3.44)	6.87 (4.62-9.11)	9.03 (5.49-12.57)	7.61 (5.70-9.52)	45.96 (40.16-51.76)	84.87 (74.02-95.72)	59.41 (54.07-64.74)
Total n=4,393	4.85 (4.55-5.15)	9.30 (8.88-9.72)	7.05 (6.79-7.31)	0.16 (0.10-0.21)	0.39 (0.31-0.48)	0.27 (0.22-0.32)	1.59 (1.42-1.76)	5.07 (4.76-5.38)	3.31 (3.13-3.48)	6.60 (6.25-6.95)	14.76 (14.23-15.28)	10.63 (10.32-10.95)
Age-standardised	4.47 (4.13-4.81)	9.72 (9.22-10.23)	6.92 (6.50-7.35)	0.14 (0.08-0.21)	0.42 (0.31-0.52)	0.27 (0.18-0.35)	1.50 (1.30-1.70)	4.99 (4.63-5.36)	3.22 (2.92-3.51)	6.12 (5.72-6.52)	15.14 (14.50-15.77)	10.41 (9.88-10.93)

Surv<30days = Survival to admission (but not to 30days); Surv30-364days = Survival to 30days or more (but not to 365days); Surv365days+ = Survival to 365days or more

Table 2: Trends over time (2002-2014) in crude and specific incidence rates (per 100,000 population per year) of OHCA arrest by long-term outcome, gender, age, remoteness, and socio-economic status in Queensland, Australia

	Surv<30days			**Surv30-364days**			**Surv365days+**			**Total admitted events**		
	Female	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*
Crude	NS	NS	NS	↑*	NS	↑*	↑**	↑***	↑***	NS	↑**	↑**
Age-group												
18-24	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
25-34	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
35-44	NS	↓*	↓*	NS	NS	NS	NS	↑*	NS	NS	NS	NS
45-54	NS	NS	NS	NS	NS	NS	↑*	↑***	↑***	NS	↑**	↑**
55-64	NS	NS	NS	NS	NS	↑*	↑*	↑**	↑***	↑**	NS	↑*
65-74	NS	↓**	↓*	NS	NS	NS	NS	NS	NS	NS	NS	NS
75-84	NS	NS	NS	↑*	NS	NS	NS	NS	NS	NS	NS	NS
85+	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Geographical Remoteness (ARIA)[1]												
Major Cities	NS	↓**	↓**	NS	NS	NS	↑*	↑***	↑***	NS	NS	NS
Inner Regional	NS	↓*	↑*	NS	NS	↑*	NS	↑**	↑**	↑***	NS	↑***
Outer Regional	NS	NS	NS	NS	NS	NS	NS	↑*	↑*	NS	NS	NS
Remote/Very Remote	NS	NS	NS	NS	NS	NS	↑*	NS	↑*	NS	NS	NS

Table 2, continued

	Surv<30days			**Surv30-364days**			**Surv365days+**			**Total admitted events**		
Socio-economic status (SEIFA)²	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*
(Lowest advantage) 1&2	NS	NS	NS	NS	NS	NS	NS	↑*	↑**	NS	NS	NS
3&4	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
5&6	NS	NS	NS	NS	NS	NS	NS	↑***	↑***	↑*	↑*	↑**
7&8	NS	NS	NS	NS	NS	NS	NS	↑***	↑***	NS	NS	NS
(Highest advantage) 9&10	NS	NS	NS	NS	NS	NS	NS	↑***	↑***	NS	NS	NS

Surv<30days = Survival to admission but not to 30days; Surv30-364days = Survival from 30-364days; Surv365days+ = Survival to 365days or more

Trend over time indicated by ↑↓ or NS (no significant trend), as follows: * p<0.05; ** p<0.01; *** p<0.001

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was mapped from residential postcode to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage of the area, lower deciles reflect lower relative advantage

Age and gender adjusted rates

When adjusted for age and gender, incidence of survival to 365days+ significantly increased (p<0.001), survival to <30days decreased significantly (p=0.001), and no trends were observed in survival to 30-364days. The remainder of the results focus on survival to 365days+, although data are presented in tables and figures for all outcomes.

Age and gender-specific rates

Incidence of total admitted events and each outcome separately was significantly greater in males than females (Table 1). Incidence increased incrementally with age-group across all outcomes (Table 3).

Table 3: Rate ratios and 95% CI of adult OHCA, by long-term outcome, gender, geographical remoteness and socio-economic status

	Surv<30days n=2,913	**Surv30-364days n=113**	**Surv365days+ n=1,367**	**Total admitted events n=4,393**
Gender				
Female n=1,379	Reference group			
Male n=3,014	RR 1.92 (1.78-2.07)	RR 2.48 (1.65-3.72)	RR 3.19 (2.82-3.61)	RR 2.24 (2.10-2.38)
Age-group				
18-24 n=13	Reference group			
25-34 n=28	RR 0.70 (0.28-1.77)	0	RR 4.45 (1.32-15.04)	RR 1.51 (0.78-2.92)
35-44 n=211	RR 7.97 (4.04-15.75)	RR 2.05 (0.21-19.71)	RR 23.47 (7.45-73.96)	RR 11.09 (6.34-19.42)
45-54 n=605	RR 24.03 (12.38-46.63)	RR 11.65 (1.54-87.84)	RR 70.87 (22.72-221.01)	RR 33.89 (19.56-58.70)
55-64 n=950	RR 55.93 (28.95-108.05)	RR 17.02 (2.28-127.12)	RR 110.17 (35.37-343.15)	RR 65.45 (37.86-113.14)
65-74 n=1,059	RR 111.51 (57.78-215.19)	RR 36.49 (4.95-268.93)	RR 148.78 (47.73-463.78)	RR 114.34 (66.17-197.57)

Table 3, continued

	Surv<30days n=2,913	Surv30-364days n=113	Surv365days+ n=1,367	Total admitted events n=4,393
75-84 n=1,051	RR 221.11 (114.64-426.48)	RR 70.38 (9.59-516.64)	RR 163.41 (52.26-510.91)	RR 196.20 (113.54-339.03)
85+ n=476	RR 296.68 (153.23-574.42)	RR 128.11 (17.15-956.98)	RR 137.10 (43.02-436.94)	RR 246.89 (142.30-428.33)
Geographical remoteness (ARIA)[1]				
Major Cities n=2866	Reference group			
Inner Regional n=878	RR 0.84 (0.77-0.93)	RR 1.47 (0.95-2.27)	RR 1.15 (1.01-1.30)	RR 0.95 (0.88-1.02)
Outer Regional n=550	RR 0.75 (0.67-0.84)	RR 1.28 (0.76-2.13)	RR 0.92 (0.78-1.08)	RR 0.82 (0.74-0.89)
Remote/Very Remote n=95	RR 0.81 (0.63-1.03)	RR 0.38 (0.05-2.74)	RR 0.80 (0.55-1.16)	RR 0.79 (0.65-0.97)
Socio-economic status (SEIFA)[2]				
***Least advantaged* 1&2 n=858**	Reference group			
3&4 n=776	RR 0.84 (0.75-0.95)	RR 0.89 (0.48-1.68)	RR 0.87 (0.73-1.04)	RR 0.85 (0.77-0.94)
5&6 n=863	RR 0.78 (0.69-0.87)	RR 1.07 (0.60-1.91)	RR 0.92 (0.77-1.09)	RR 0.83 (0.75-0.91)
7&8 n=1330	RR 1.18 (1.06-1.31)	RR 1.57 (0.91-2.69)	RR 1.38 (1.18-1.61)	RR 1.25 (1.14-1.36)
***Most advantaged* 9&10 n=561**	RR 0.67 (0.58-0.76)	RR 0.50 (0.23-1.10)	RR 0.89 (0.74-1.08)	RR 0.73 (0.66-0.81)

Surv<30days = Survival to admission (but not to 30days); Surv30-364days = Survival to 30days or more (but not to 365days); Surv365days+ = Survival to 365days or more

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)
[2]SEIFA (Socioeconomic Index For Areas) was mapped from residential postcode to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage of the area, lower deciles reflect lower relative advantage

When stratified by age and gender (Table 2), rates of survival to 365days+ increased significantly over time in males and females in the 45-64year groups ($p<0.001$) and in males (but not females) in the 35-44year group ($p=0.025$). There were no trends over time in the 18-34year or 65year+ age-groups, for either males, females, or males and females combined.

Geographical remoteness (ARIA) and socio-economic status (SEIFA)

Incidence of total admitted events in inner regional, outer regional, remote/very remote areas was lower than in major cities (Table 3). Incidence of total events decreased as remoteness increased. Survival to 365days+ was significantly higher in inner regional areas compared with major cities, but while rates were lower in outer regional areas and remote/very remote areas than in major cities, these differences were not significant.

After adjusting for remoteness and gender, there were significant increases over time in total admitted events ($p=0.002$), and survival to 365days+ ($p<0.001$).

Figure 2 shows temporal trends in OHCA by remoteness. Survival to 365days+ increased significantly over time in all remoteness categories (Figure 2). Survival to 365days+ increased significantly over time in females ($p=0.046$) and males ($p<0.001$) in major cities; males (not females) in inner regional ($p=0.009$) and outer regional areas ($p=0.012$); and females (not males) in remote/very remote areas ($p=0.020$) (Table 2).

An inverse association between SES and total events was observed, except in SEIFA category 7&8, where incidence of total events was paradoxically highest (Figure 3). This was observed for every outcome.

After adjusting for SES and gender, there were significant increases over time in total admitted events (p=0.003), and survival to 365days+ (p<0.001). Survival to 365days+ increased significantly over time for all SEIFA categories, except 3&4. When results were stratified by SES-and gender, significant increases were observed in survival to 365 days+ in males (but not females) in all SEIFA categories (1&2: p=0.010; 5&6, 7&8 and 9&10: p<0.001), except SEIFA category 3&4. There were no significant trends observed in females in any SEIFA category. Total admitted events increased significantly over time in males (p=0.016) and females (p=0.033) of SEIFA 5&6 (Table 2).

Table 4 presents annual incidence rates and 95% confidence intervals by remoteness, socio-economic status, gender and outcome. Table 5 presents annual age-standardised incidence rates by remoteness and socio-economic status, gender and outcome.

Table 4: Adult OHCA incidence rates by remoteness, socio-economic status and long-term outcome in Queensland, Australia (per 100,000 population per year), 2002-2014

Geographical Remoteness (ARIA)[1]	**Surv<30days n=2,909**			**Surv30-364days n=113**			**Surv365days+ n=1,367**			**Total admitted events n=4,389**		
	Female n=1,014	*Male n=1,895*	*Total n=2,909*	*Female n=33*	*Male n=80*	*Total n=113*	*Female n=332*	*Male n=1,035*	*Total n=1,367*	*Female n=1,379*	*Male n=3,010*	*Total n=4,389*
Major Cities **n=2,866**	5.46 (5.05-5.87)	10.43 (9.86-11.01)	7.89 (7.54-8.23)	0.12 (0.06-0.18)	0.40 (0.28-0.51)	0.25 (0.19 - 0.32)	1.52 (1.31-1.74)	5.35 (4.94-5.76)	3.39 (3.16-3.62)	7.10 (6.64-7.56)	16.18 (15.46-16.89)	11.53 (11.11-11.95)
Inner Regional **n=878**	4.65 (3.99-5.31)	8.67 (7.76-9.59)	6.64 (6.08-7.21)	0.30 (0.13-0.46)	0.45 (0.24-0.66)	0.37 (0.24-0.51)	1.89 (1.47-2.32)	5.92 (5.16-6.67)	3.89 (3.46-4.32)	6.84 (6.04-7.64)	15.04 (13.84-16.24)	10.90 (10.18-11.62)
Outer Regional **n=550**	3.72 (3.01-4.42)	8.05 (7.03-9.07)	5.93 (5.30-6.55)	0.21 (0.04-0.38)	0.43 (0.20-0.67)	0.32 (0.18-0.47)	1.91 (1.41-2.42)	4.28 (3.53-5.02)	3.12 (2.66-3.57)	5.84 (4.95-6.72)	12.76 (11.48-14.04)	9.37 (8.58-10.15)
Remote and very remote **n=95**	4.72 (2.79-6.65)	7.81 (5.48-10.15)	6.36 (4.83-7.89)	0	0.18 (0.00-0.54)	0.10 (0.00-0.29)	1.23 (0.25-2.22)	4.00 (2.33-5.67)	2.70 (1.70-3.70)	5.95 (3.78-8.12)	11.99 (9.10-14.88)	9.15 (7.31-11.00)

Table continues over page

Table 4, continued

Socio-economic status (SEIFA)[2]	**Surv<30days n=2,908**			**Surv30-364days n=113**			**Surv365days+ n=1,367**			**Total admitted events n=4,388**		
	Female n=1,014	*Male n=1,894*	*Total n=2,908*	*Female n=33*	*Male n=80*	*Total n=113*	*Female n=332*	*Male n=1,035*	*Total n=1,367*	*Female n=1,379*	*Male n=3,009*	*Total n=4,388*
1&2 n=858	5.06 (4.33-5.78)	11.14 (10.05-12.23)	8.06 (7.41-8.71)	0.16 (0.03-0.29)	0.39 (0.18-0.59)	0.27 (0.15-0.39)	1.88 (1.44-2.32)	4.85 (4.14-5.57)	3.35 (2.93-3.77)	7.10 (6.24-7.96)	16.38 (15.06-17.70)	11.68 (10.90-12.46)
3&4 n=776	5.10 (4.39-5.81)	8.51 (7.59-9.42)	6.79 (6.21-7.37)	0.18 (0.05-0.31)	0.31 (0.13-0.48)	0.24 (0.13-0.35)	1.56 (1.16-1.95)	4.28 (3.63-4.93)	2.91 (2.52-3.29)	6.83 (6.01-7.65)	13.09 (11.96-14.23)	9.95 (9.25-10.65)
5&6 n=863	4.61 (3.98-5.23)	7.99 (7.16-8.83)	6.28 (5.76-6.80)	0.20 (0.07-0.33)	0.39 (0.20-0.57)	0.29 (0.18-0.40)	1.26 (0.93-1.58)	4.94 (4.28-5.59)	3.07 (2.71-3.43)	6.06 (5.34-6.78)	13.32 (12.24-14.39)	9.64 (9.00-10.28)
7&8 n=1,330	6.06 (5.35-6.77)	13.06 (12.01-14.11)	9.52 (8.88-10.15)	0.17 (0.05-0.29)	0.69 (0.45-0.93)	0.43 (0.29-0.56)	2.08 (1.66-2.49)	7.23 (6.44-8.01)	4.62 (4.18-5.06)	8.31 (7.48-9.14)	20.98 (19.64-22.31)	14.56 (13.78-15.35)
9&10 n=561	4.08 (3.40-4.76)	6.75 (5.85-7.65)	5.39 (4.83-5.95)	0.09 (0.00-0.19)	0.19 (0.04-0.33)	0.14 (0.05-0.23)	1.43 (1.02-1.83)	4.61 (3.87-5.35	2.99 (2.57-3.41)	5.60 (4.80-6.40)	11.55 (10.38-12.72)	8.52 (7.81-9.22)

Surv<30days = Survival to admission (but not to 30days); Surv30-364days = Survival to 30days or more (but not to 365days); Surv365days+ = Survival to 365days or more

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was mapped from residential postcode to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage of the area, lower deciles reflect lower relative advantage

Table 5: Age-standardised incidence rates by remoteness and socio-economic status and long-term outcome in Queensland, Australia (per 100,000 population per year)

	Surv<30days			Surv30-364days			Surv365days+			Total admitted events		
	Female	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*	*Female*	*Male*	*Total*
Geographical Remoteness (ARIA)[1]												
Major Cities	5.08	11.27	7.92	0.11	0.44	0.25	1.46	5.48	3.40	6.66	17.19	11.56
Inner Regional	3.81	7.82	5.72	0.23	0.43	0.33	1.59	5.15	3.36	5.64	13.42	9.41
Outer Regional	3.79	8.82	6.29	0.22	0.41	0.32	1.96	4.26	3.14	5.97	13.48	9.75
Remote & Very Remote	5.33	9.43	7.36	0	0.41	0.09	1.27	4.07	2.76	6.60	13.65	10.20
Socio-economic status (SEIFA)[2]												
(Lowest advantage) 1&2	4.15	10.27	7.05	0.13	0.37	0.24	1.63	4.45	3.02	5.91	15.09	10.31
3&4	4.28	8.12	6.09	0.15	0.30	0.22	1.41	3.99	2.69	5.83	12.41	9.00
5&6	4.12	8.20	6.01	0.19	0.39	0.28	1.15	4.73	2.90	5.46	13.32	9.19
7&8	6.35	15.38	10.57	0.19	0.83	0.46	2.15	7.70	4.88	8.69	23.91	15.91
(Highest advantage) 9&10	4.61	8.54	6.39	0.08	0.22	0.15	1.50	5.22	3.28	6.19	13.99	9.82

Surv<30days = Survival to admission but not to 30days; Surv30-364days = Survival from 30-364days; Surv365days+ = Survival to 365days or more

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was used to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage of the area, lower deciles reflect lower relative advantage

DISCUSSION:

This study is the first to report annual incidence and trends over time in OHCA by long-term outcomes (survival to admission, survival to 30-364days, and survival to 365days+) and shows that, of those patients who survive to admission, survival to 365days+ has improved. Previous studies[14, 15] investigated trends over time in incidence of outcomes up to hospital arrival only, which is less informative to strategy evaluation and development. The purpose of this paper was to investigate longer-time survival in patients once their pre-hospital experience is complete, and how factors such as age, gender, remoteness and socioeconomic status may influence these outcomes, hence this study is a novel and important addition to the literature.

Overall / age gender

Of those who survive to hospital admission, the majority die within 30days (IR: 6.92; 95%CI: 6.50-7.35), however, this rate did not change over time (i.e., the proportion of those dying within 30days of admission to hospital remained the same over the 13 year study period). Conversely, the incidence of those surviving beyond 365days+ did increase over the study period, consistently in crude, gender-specific and all adjusted rates (age+gender, remoteness+gender and SES+gender). This is the longest-term outcome measured by incidence in the literature and provides a very firm indication that quality of treatment has improved. Annual crude incidence rate of total OHCA events in Queensland was previously reported by the authors (73.95 per 100,000 per annum; 72.61 age-standardised), and increased significantly over the study period. Incidence of sustained ROSC also increased over time, suggesting an improvement in quality of pre-hospital treatment in this cohort.[16] The observed increase in this paper of survival to 365days+ provides a further level of validation to the notion of improved pre-hospital care. The key to cardiac arrest survival is multiple systems working efficiently and synchronously, so it is most likely this result has been achieved in combination with improvements in other areas of the OHCA patient pathway, such as emergency department, intensive care and rehabilitation services.

The significant decrease over time of survival to <30days in age+gender adjusted incidence, is likely a reflection of the increase in survival to 365days+, particularly alongside no significant change in incidence of survival to 30-364days or total events. This means fewer patients are dying before 30days and more patients are surviving past 365days, providing further validation for the increase in the quality of care, including improved selection of appropriate patients on which to attempt resuscitation.

Age is a predictor of outcome, so it is unsurprising that the increase in incidence of survival to 365days+ over time was largely attributable to age groups incorporating 45-64 years. The younger groups in which no significant change was found, is likely due to smaller number of events in these groups and consequent reduced power.

Interestingly, although there were no significant changes in survival to 365days+ in age groups of 65 years+, rates of survival to 30-364days did increase in females aged 75-84years. Further investigation into this is required.

There were few patients in the survival to 30-364days group (n= 113; 2.5% of those who survived to admission). To date, the most commonly referred to longer-term outcome measures are “survival to admission”, “survival to 30days”, and “survival to 365days”. However, this leaves a group of patients in the middle, which are largely unexplored (survival from 30-364days). We intentionally included this group in this paper in order to explore whether they differ from those who survive < 30days, or 365days+. The analyses presented here indicate that there may be characteristics unique to this group of people, however the very small size of this group limits interpretability. This also highlights uncertainty about the most useful end points for long-term outcome, which should be explored further with survival analysis.

Geographical remoteness

The cohort of this study consists of cases that survived to hospital admission or beyond. Therefore, it is an expected finding that the rate of total events decreases as remoteness increases. This is in accordance with previous studies suggesting preferred outcomes are more likely to occur in less remote locations.[15, 16] This is the likely result of longer response times and less access to tertiary health care services.[25]

A positive finding is the increase over time in Survival to 365days+ apparent in males+females within all remoteness categories. This may be an indication that strategies aimed at improving outcomes from OHCA have penetrated more remote areas, as well as the less remote and is concurrent with the findings of a previous study.[16] Addressing health care in more remote areas has been a point of focus for some time and this study further demonstrates good progress to date. Nevertheless, in order to maintain this, it is important this area remains a point of focus and this work is continued.

An interesting finding in females is an increase in incidence of Survival to 365days+ over time in the remote/very remote category, but the lack of increase over time in the inner or outer regional areas. It seems odd that strategies to improve OHCA outcomes may have penetrated females in remote/very remote areas, but not in inner and outer regional areas. Additionally, if insufficient power were the cause, it would be expected that this would also be observed in the remote/very remote category (fewer people in the sample). It may be the promotion of strategies for more remote areas has been successful, but at the same time focused, resulting in a lack of improvement in the mid-remoteness categories (inner and outer regional areas). This finding requires further investigation.

Socio-economic status

The increase over time in incidence of Survival to 365days+ in most SES categories (all but SEIFA 3&4) is a further positive finding and suggestive that strategies have penetrated all levels. Australia has a universal health care system, so it seems unlikely that successful strategies simply did not penetrate those in SEIFA 3&4 to the same extent as those in the surrounding SES categories, thus it is probable an alternative explanation exists. The clear disparity in Survival to 365days+ between genders within the SES-gender analyses (nil changes over time in any SES category in females) is an interesting finding. This may be due to insufficient power in some cases but may also be an indication that future strategies require a more female or non-gender specific focus.

The finding that people in areas categorized as high (but not the highest) advantage (SEIFA 7&8) experienced the highest incidence of every outcome was also demonstrated in a previous study of shorter-term outcomes.[15] This finding requires further investigation.

Strengths and limitations

The major strengths of this retrospective cohort study are the population-based approach to calculate incidence of outcomes and the linking of three large reputable datasets, as previously reported.[15, 16] Data linkage firstly allowed access to multiple sources for the same variables (such as age, gender and postcode) and therefore collation of a more accurate and complete dataset; and secondly, access to additional information such as the long-term outcomes specific to this study. Additionally, this method avoids high loss to follow up rates (99.2% data linkage sensitivity). Measurement and selection bias were very unlikely in this study as routinely collected data were used to capture every OHCA of cardiac aetiology in adult residents of Queensland attended by QAS during the study period.

Limitations have also previously been reported[15, 16] and include dataset quality at source; the presence of unknown confounders; using residential postcode to estimate SES and geographical remoteness; and the inherent biases of observational studies. Of particular relevance to this paper is the use of postcodes to estimate socio-economic status via the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) developed by the Australian Bureau of Statistics. Postcodes are 4 digit numbers created by the Australian Postal service to assist with mail delivery. While there are no data available on the geographic boundaries or population size of postcodes, the Australian Bureau of Statistics has developed a method for estimating population size that approximates the regions defined by postcodes. During the time period of this data collection (2002-2014), SLAs (statistical local areas) were the closest approximation to postcodes and consequently, of geographical areas for which population data could be obtained. In 2007 (approximately the mid-point of the data collection period), there were close to 500 postcodes (and therefore SLAs) in Queensland, each encompassing varying geographic distances, and including populations ranging from 7 to 79,150[26]. Consequently, it is acknowledged that IRSAD is an aggregated area-level measure of socioeconomic disadvantage, and therefore may not accurately represent the socio-economic status of all individuals living in the area. However, there are no other data contained within the routinely collected data sets available in Queensland that could be used as an alternative measure. More sophisticated analyses involving the association between socio-economic status and long-term outcomes from OHCA would only be possible through a prospective study design, where another more accurate and reliable measure of socio-economic status could be purposefully collected from individuals.

The sample size in this paper was substantially lower than the previous pre-hospital studies[15, 16] and therefore presence of type 2 error in some groups was greater. Additionally, no cases beyond 2014 and no quality of life measures were captured. Only confirmed Queensland residents were included in this study. Imposing this case selection criteria was essential to facilitate calculation of incidence (and in particular, incidence by socio-economic status and geographical remoteness, which were mapped from postcode data), but means those with no residential address such as the homeless, were not accounted for. Many results described here require further investigation using different study designs in order to elucidate explanations for the observed associations. This was beyond the scope of the current study, which was exploratory in nature and designed to investigate the incidence and temporal trends of long-term outcomes of adult OHCA by age, gender, geographical remoteness and SES. The intent was to contribute to the poor evidence in this sphere, and should be considered a platform from which new ideas can be generated using different, more appropriate (and sophisticated) study designs and measures that likely do not rely on routinely collected data. As described above, a prospective study design could be used to more specifically investigate the association between SES and outcomes from OHCA. The authors are currently involved with two separate pieces of work involving this cohort using different analytical techniques (e.g., survival analyses and multinomial logistic regression), to identify predictors of outcome.

CONCLUSION:

Incidence in survival to 365days or more in adults post OHCA of presumed cardiac aetiology has significantly increased over the time period of this study. This suggests that health care strategies implemented to improve outcomes from OHCA have been successful, including those delivered in the pre-hospital environment. Encouragingly, there is also evidence to suggest that strategies are penetrating groups living in more remote locations and the lower socio-economic groups, however, it is important focus continues in those areas. Population subsets requiring further investigation include females in inner and outer regional areas, in which there were no trends in survival to 365days or more; and SEIFA 7&8 which presented with the highest incidence of every outcome.

We recommend the ongoing reporting of long-term outcomes from OHCA is undertaken using population-based incidence; additionally, survival analyses be undertaken to investigate the most informative time measure of long-term survival.

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CONTRIBUTORSHIP STATEMENT: KP and KW were responsible for the conceptual design of the study, with input from the other authors. KP performed the data analysis with assistance from KW. KP was responsible for drafting the manuscript which was critically reviewed by KW. All authors contributed critical revision and editing of the final manuscript.

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COMPETING INTERESTS: None declared.

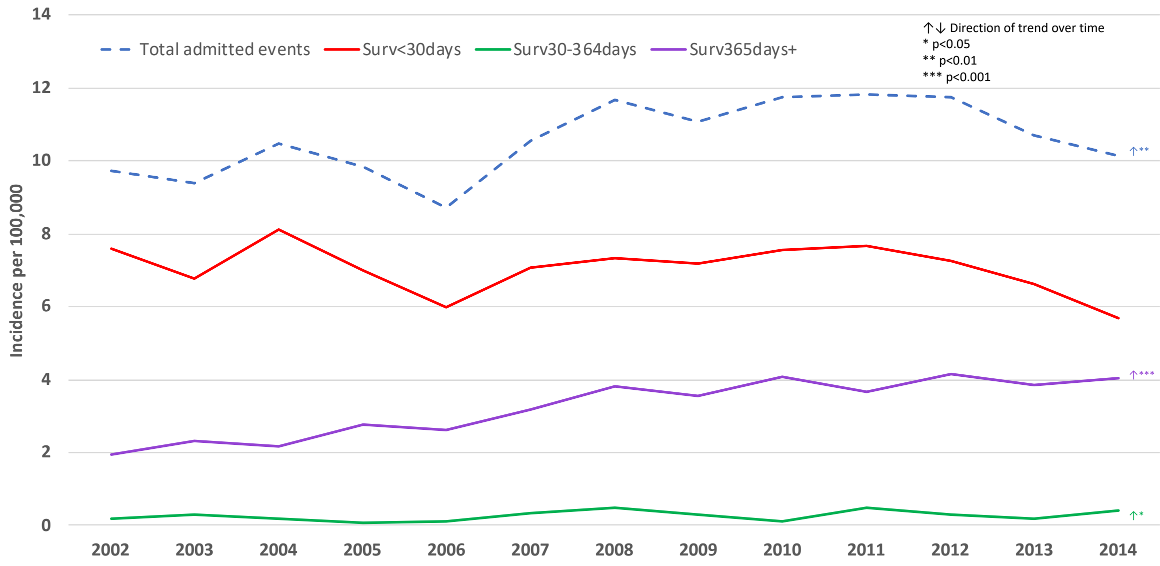

Figure 1: *Crude incidence of adult (18 years+) OHCA of cardiac aetiology, by outcome, over time* (per 100,000 population)

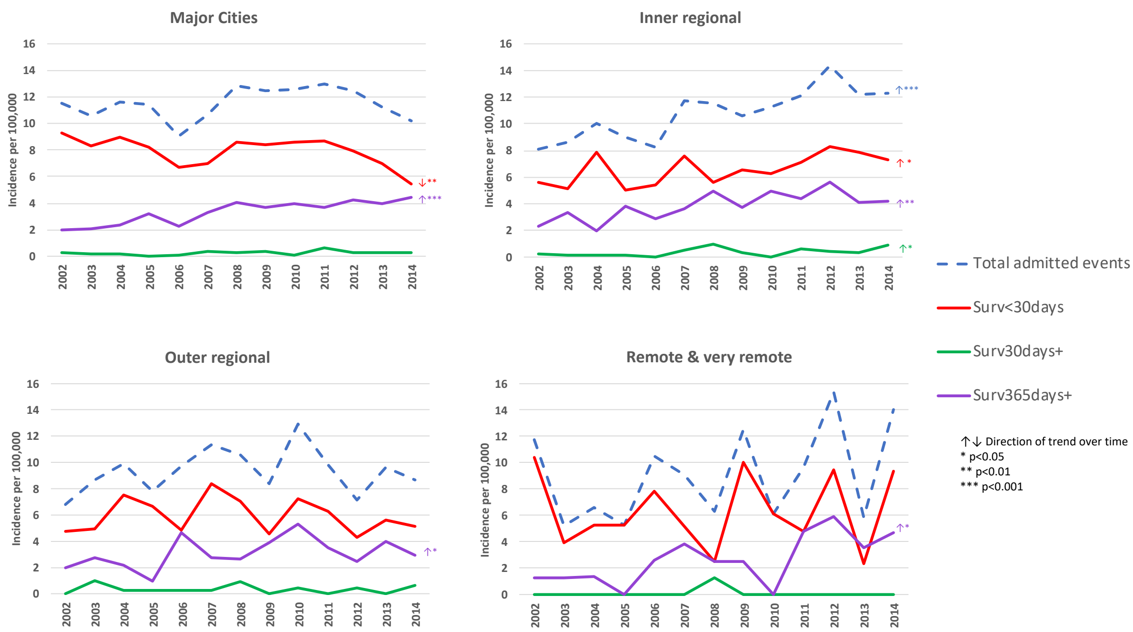

Figure 2: *Incidence of adult (20 years+) OHCA of cardiac aetiology, by outcome and geographical remoteness (per 100,000 per annum)*

Figure 3: *Incidence of adult (20 years+) OHCA of cardiac aetiology, by outcome and socio-economic status (per 100,000 per annum)*

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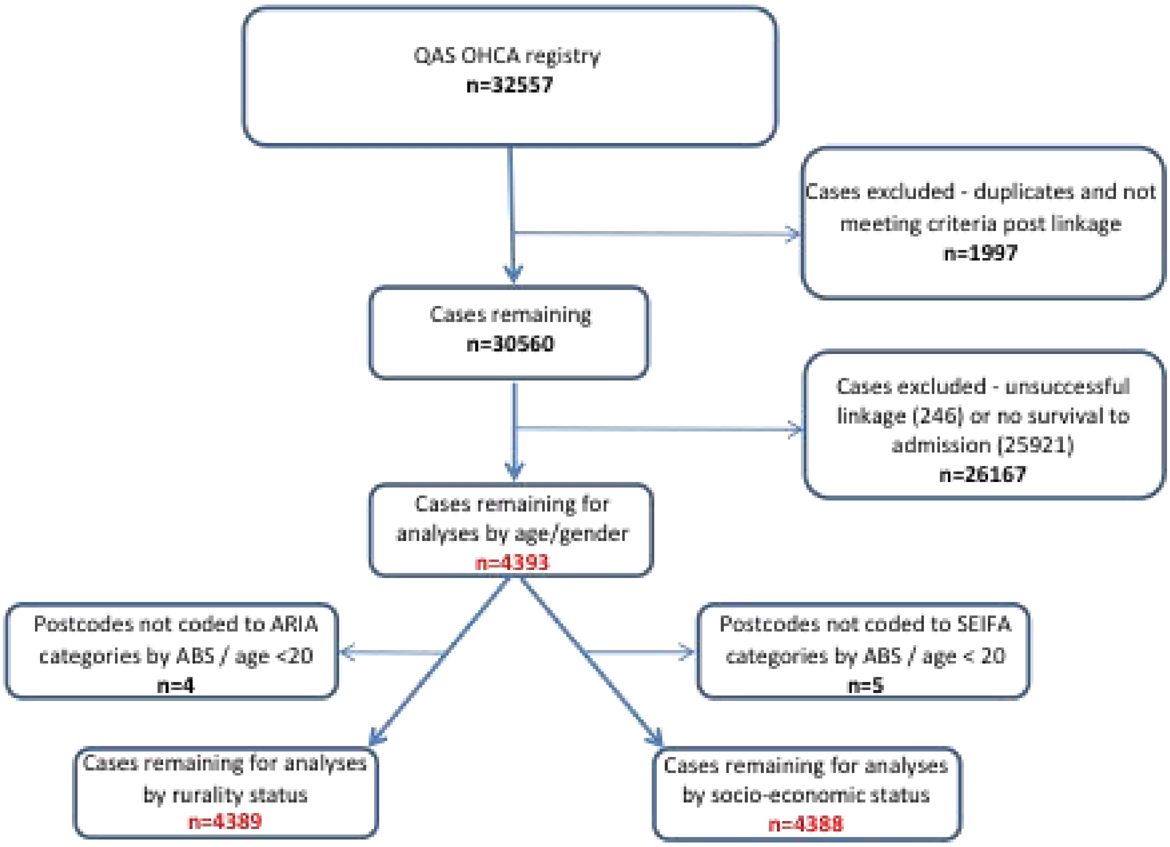

Supplemental Figure 1: *Flowchart to show inclusion and exclusion criteria for sample data*

6.3 Additional Analyses

Temporal trends of incidence of total events and by outcome were calculated adjusting for age & gender, ARIA & gender and SEIFA & gender, but these rates were not reported in the publication due to publishing constraints. These rates are presented in Table 4 below for interest.

Table 6: Trends over time (2002-2014) in adjusted incidence rates, by long-term outcome in Queensland, Australia

	Surv<30days	**Surv30-364days**	**Surv365days+**	**Total events**
Age & gender adjusted	↓**	NS	↑***	NS
ARIA[1] & gender adjusted	NS	↑*	↑***	↑**
SEIFA[2] & gender adjusted	NS	↑*	↑***	↑**

Surv<30days = Survival to admission but not to 30 days; Surv30-364days = Survival from 30-364 days; Surv365days+ = Survival to 365 days or more

Trend over time indicated by ↑↓ or NS (no significant trend), as follows: * p<0.05; ** p<0.01; *** p<0.001

[1]Location of usual residence was categorised using ARIA (Accessibility/Remoteness Index of Australia), developed by National Centre for the Social Applications of Geographic Information Systems (GISCA) [20]. Each geographical area was allocated a score between 0 and 15, based on the (road) distance to nearby towns that provide services. Scores were then allocated to the following categories [21]: major city: 0.0–0.2; inner regional: 0.2–2.4; outer regional: 2.4–5.92; remote: 5.92–10.53; very remote: 10.53+)

[2]SEIFA (Socioeconomic Index For Areas) was used to estimate socioeconomic status in this study - specifically, the Index of Relative Socioeconomic Advantage and Disadvantage [22]. Higher deciles reflect higher relative advantage, lower deciles reflect lower relative advantage

6.4 Chapter Summary

- This is the first study known to the authors to report temporal trends in OHCA incidence by long-term outcome.
- Annual crude incidence per 100,000 per annum was 10.63 (95%CI: 10.32-10.95) for total events; 7.05 (95%CI: 6.79-7.31) for survival <30 days; 0.27 (95%CI: 0.22-0.32) for Survival 30-364 days; and 3.31 (95%CI: 3.13-3.48) for survival beyond 365 days.
- Crude incidence of total OHCA events resulting in hospital admission, survival to 30-364 days and survival beyond 365 days increased significantly over time, but no trends were observed for patients who survived <30 days. The same results were mostly observed for gender-specific rates.
- Rates of long-term survival (365 days+) increased over time in crude analyses, and also after adjusting for gender, age+gender, remoteness+gender and socio-economic status+gender). This indicates that quality of treatment has improved.
- The increased incidence of survival beyond 365 days over time was most pronounced in age groups incorporating 45-64 years, for both males and females.
- Rates of survival to 30-364 days increased in females aged 75-84 years.
- Rates of survival to 365 days+ was significantly higher in inner regional areas compared with major cities, but lower in outer regional areas and remote/very remote areas than in major cities (though these trends were not significant).
- Survival to 365 days+ increased significantly over time in all remoteness categories. This is an indication that strategies aimed at improving outcomes from OHCA have penetrated more remote areas, as well as the less remote.
- Survival beyond 365 days increased significantly over time for all SEIFA categories, (except 3&4), suggesting strategies have penetrated all levels. The lack of observed change in SEIFA 3&4 requires further exploration.
- There were few patients in the group whose OHCA resulted in survival 30-364 days, highlighting uncertainty about the most useful end point for long term outcome. Survival analysis would usefully inform this further.

6.5 Final Word (Chapter 6)

This study is the final Chapter in the thesis to address aim 2 (To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia) and reports the incidence and temporal trends of long-term outcomes of adult OHCA of cardiac aetiology. This Chapter provides a novel and informative addition to the literature. Incidence rates were adjusted for some factors (such as age, gender, geographical remoteness and socio-economic status), but it was not possible to adjust for further known potential confounding factors. The next Chapter (Chapter 7, publication 6) is designed to address this gap and identify independent pre-hospital risk factors of adult OHCA of cardiac aetiology using multivariate analyses.

Chapter 7: Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics

7.1 Overview

This Chapter addresses aim 3 of the thesis and comprises the sixth and final publication. Independent pre-hospital predictors of short and long-term outcomes from OHCA of presumed cardiac aetiology are explored. This work complements the previous Chapters of this thesis which explore the epidemiology and trends over time in incidence of pre-hospital and longer-term outcomes from OHCA by age, gender, geographical remoteness and SES (Chapters 4-6, Publications 3-5).

To date, no known published studies using multivariate analyses to predict outcomes from OHCA have been undertaken in Australasia. Additionally, this is the first time pre-hospital identified patients have been accessed with a primary purpose to provide pre-hospital relevant predictive factors of long-term outcomes of non-traumatic OHCA. This study will inform pre-hospital service provision in Queensland and other areas with developed health care services.

This Chapter builds on previous chapters in this thesis (Chapters 4-6, Publications 3-5), and focuses only on patients who received a resuscitation attempt. This cohort was selected to be clinically meaningful, as they are the most informative for pre-hospital strategy development. Analysis relating to the cohort who did not receive a resuscitation attempt would better inform community-based strategies, but this is outside of the scope of this thesis. The purpose of this chapter is to inform pre-hospital health care policy development and service provision in Queensland.

This study included all adult residents of Queensland, who suffered an OHCA of presumed cardiac aetiology and had resuscitation attempted by QAS paramedics in

Queensland (15,142). Four mutually exclusive outcomes were used, that differ slightly from outcomes described in previous Chapters:

- No pre-hospital ROSC sustained to ED or ROSC in ED (-ROSC to/in ED): This group had either no ROSC at any stage or pre-hospital ROSC that was not sustained to ED and was not re-established in ED. This is the least preferred outcome
- Pre-hospital ROSC sustained to ED or ROSC in ED – survival to 29 days (+ROSC to/in ED): This group had either pre-hospital ROSC sustained to ED or ROSC achieved in ED. This group also died in 29 days or less post the OHCA event
- Survival to 30-364 days (Surv30-364days) - this group survived to 30-364 days post the OHCA event
- Survival to 365 days or more (Surv365days+): This group survived to 365 days or more post the OHCA event. This is the most preferred outcome

Figure A shows the position of this Chapter in the thesis.

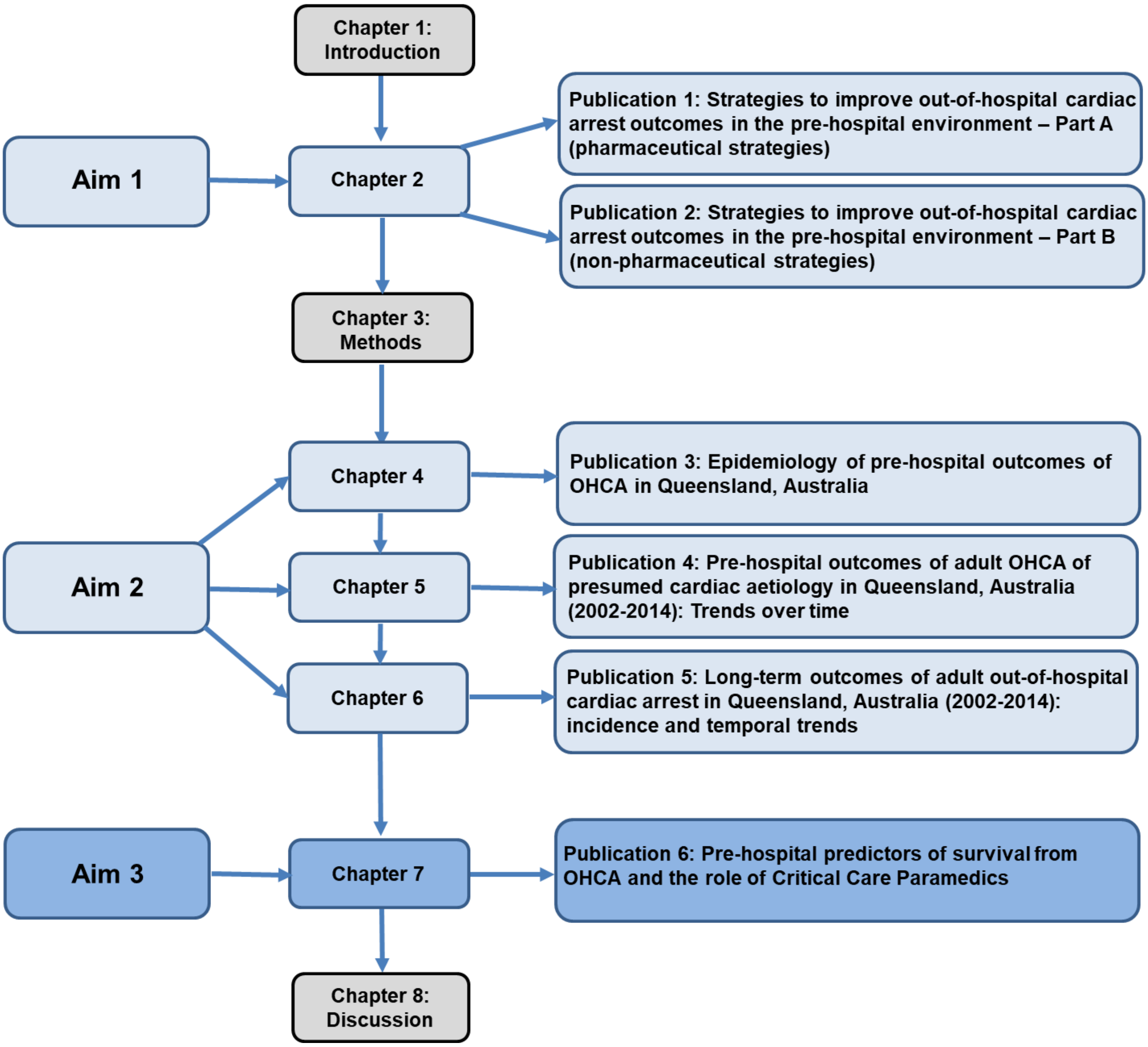

Figure A: Conceptual model of thesis – Aim 3, Chapter 7, Publication 6

7.2 Manuscript

This Chapter comprises the following manuscript that will be submitted to a peer-reviewed journal:

Pemberton K. and Watt K. Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics. *In preparation.*

This article is inserted in the format required by the journal to which the manuscript will be submitted for review.

Title:

Pre-hospital predictors of survival from OHCA and the role of Critical Care Paramedics

Abstract:

Objective: To identify independent predictors of short and longer-term outcomes from adult out-of-hospital cardiac arrest (OHCA) of presumed cardiac aetiology, that received a resuscitation attempt by Queensland Ambulance Service (QAS) paramedics between 2002-2014 in Queensland, Australia.

Methods: This is a retrospective cohort study in which three large routinely collected databases were linked: 1) QAS OHCA Registry (case identifying database); 2) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and 3) Queensland Registrar General (RG) Death Registry. Inclusion criteria were adult (18years+) residents of Queensland, who suffered an OHCA of presumed cardiac aetiology and had resuscitation attempted by QAS paramedics. Four mutually exclusive outcomes were analysed: 1) No pre-hospital ROSC sustained to ED or ROSC in ED (-ROSC to/in ED); 2) Pre-hospital ROSC sustained to ED or ROSC in ED – survival to 29 days (+ROSC to/in ED)); 3) survival to 30-364 days (Surv30-364days); and 4) survival to 365 days or more (Surv365days+). Multinomial logistic regression was used to calculate odds ratios and 95% confidence intervals.

Results: There were 15,142 cases that met inclusion criteria. Variables positively (and significantly) associated with survival to 365 days after adjusting for all relevant confounders are: an initial shockable rhythm; bystander witnessed events with bystander CPR; paramedic witnessed events; intubation placement; time of day (midday-2.59pm); and CCP attended scene.

Conclusion: From a service provision perspective, attendance of a CCP at an OHCA may be an important factor to achieve preferred long-term outcomes. Enhanced experience, exposure and expertise are potential causes so strategies which optimise on these should be investigated and implemented when feasible.

Introduction:

Out-of-hospital cardiac arrest (OHCA) is a major health problem worldwide. Survival is generally low, but some recent studies have shown improvements, which has renewed interest in ways to improve survival more broadly. Identifying predictors and risk factors of outcome informs policy and guidelines to optimise outcomes.

A large systematic review and meta-analysis to identify predictors of survival from OHCA incorporating 79 studies over more than 30-years, reported that survival to hospital discharge was associated with events that were bystander or Emergency Medical Service (EMS) witnessed, had bystander cardiopulmonary resuscitation (CPR), an initial shockable rhythm and return of spontaneous circulation (ROSC) in the field[1]. Since then, three published studies have undertaken multivariate logistic regression to identify independent risk factors of non-traumatic OHCA outcomes[2-4]. One[2] included only patients that survived to ICU admission and identified 10 predictors of poor outcome (CPC 3-5) at 6 months, including 6 identifiable pre-hospital (older age, CA at home, initial rhythm non-shockable, longer duration of no flow, longer duration of low flow and adrenaline administration). Another study[3], including patients that survived to hospital discharge only, found pre-hospital identifiable independent risk factors of mortality at 1- and 3-years to be older age, previous cancer and non-shockable initial rhythm. Due to inclusion criteria, these studies both had a limited sample size (933 and 1591 respectively). The third study used pre-hospital identified cases and aimed to compare determinants of survival to hospital admission and discharge for traumatic and non-traumatic OHCA[4]. Age, response time and adrenaline administration were inversely associated with both survival to admission and discharge for non-traumatic OHCA, while shockable rhythm, witnessed cases and the attendance of an air ambulance were positively associated. Males had a survival disadvantage to admission, but advantage to discharge, and patients who were intubated had an advantage to admission, but disadvantage to discharge.

The association between ALS (skills include intubation, IV and IO access and ACLS medication administration), response interval and clinical outcome for non-traumatic OHCA was investigated in another study[5]. For each one minute of increased ALS response, survival to discharge and favourable neurological outcome significantly decreased. This analysis included adjusting for the response interval from first EMS contact, usually BLS (skills include chest compressions, BVM ventilation and AED use).

Other studies investigating predictive factors of ED survival[6] and survival to 90 days[7] after cardiac arrest, found associations with younger age, initial shockable rhythm and short CPR durations.

Comparability across these few published (mainly European) studies[2-7] is prohibited by different case inclusion criteria (e.g., pre-hospital vs ICU), and inconsistent outcome measures (survival to discharge vs survival to 30 days vs survival to 1 year or 3 years). To date, no multivariate studies to predict outcomes from OHCA have been undertaken in Australasia.

Previous studies in Queensland report the incidence rates by outcome of OHCA by various characteristics such as age, gender, geographical remoteness and socioeconomic status, as well as trends over time[8-10]. Increased rates of OHCA and poorer outcomes were generally observed for increasing age, being male, increasing remoteness and lower socio-economic status, though some exceptions were noted. Specifically, cases living in areas identified as the 2nd most advantaged SES category (SEIFA 7&8) experienced the highest incidence of OHCA overall and by every outcome. Incidence of the most preferred outcomes (sustained ROSC and survival to 365 days+) increased over time overall and mostly when stratified by remoteness and SES. Again, there were some exceptions. No significant trends over time were observed in rates of sustained ROSC for cases living in remote areas, nor for survival to 365 days+ for the cases living in areas identified as the 2nd most disadvantaged SES category (SEIFA 3&4). The purpose of this study is to build on these three epidemiological papers derived from a population-based retrospective cohort study through linkage of three routinely collected administrative data sets to investigate the independent predictors of outcomes from OHCA, while adjusting for relevant confounders.

The Queensland Ambulance Service has been described previously[11]. Where resources allow, OHCA cases routinely receive two Advanced Care Paramedic (ACP) crews (skills include LMA placement and IV fluid/adrenaline administration), backed up by a Critical Care Paramedic (CCP) as a single responder (skills include intubation, IO access and critical care drugs and procedures).

The aim of this study is to identify independent predictors in the pre-hospital environment of short and longer-term outcomes from adult OHCA of presumed cardiac aetiology, that received a resuscitation attempt by QAS paramedics between 2002-2014 in Queensland, Australia. This is the first study using pre-hospital identified patients with a primary purpose to provide pre-hospital relevant predictive factors of long-term outcomes of non-traumatic OHCA and adjusts for as many potential confounders as possible. Additionally, this is the first time geographical remoteness, SES, time of day, day of week and CCP attendance have been investigated in this way. This study will inform future pre-hospital service provision, including policy/guideline/strategy development and paramedic decision making.

Method:

Three large routinely collected population-based databases were linked in this retrospective cohort study. These were: 1) QAS OHCA Registry; 2) Queensland Hospital Admitted Patient Data Collection (QHAPDC); and 3) Queensland Registrar General (RG) Death Registry. The QAS OHCA Registry was used to identify cases for linkage. Inclusion/exclusion criteria[9] and the methods for data linkage and collation have been previously reported[9, 10]. In this study, additional cases were excluded if they did not receive a resuscitation attempt by QAS paramedics (n=15418), to provide the most informative cohort for pre-hospital strategy development. While analysis of the cohort that did not receive a resuscitation attempt would better inform community-based strategies, this is outside the scope of this study. Data linkage allowed for a more accurate and complete dataset for analysis, as previously described[10]. Of most relevance is that inclusion of QHAPDC and RG Death Registry data allow assessment of longer-term outcomes from OHCA, which is not possible using QAS OHCA Registry. Additionally, variables such as residential postcode were included, which allowed investigation of geographical remoteness and SES in more detail, as the completeness and accuracy of these variables is higher in QHAPDC and RG Death Registry than in QAS OHCA Registry.

Independent variables were classified into four groups: 1) Demographic (age, gender, residential postcode, which was mapped to SES (via Socioeconomic Index For Areas - SEIFA, specifically Index of Relative Socioeconomic Advantage and Disadvantage, with higher deciles reflecting higher relative advantage)[12] as well as geographical remoteness (via Accessibility/Remoteness Index of Australia)[13 14]; 2) Clinical (initial rhythm; shockable status; pre-QAS shocks; number QAS shocks; QAS shocks; witnessed arrest/bystander CPR; intubated; laryngeal mask airway (LMA); adrenaline); 3) Event-based (day of week, time of day, season) and 4) System-based (Critical Care Paramedic attended, response interval). Note that witnessed arrest and bystander CPR variables were amalgamated into one variable to manage paramedic witnessed cases, in which bystander CPR could not be expected. Cases with an unknown entry on either witnessed status or bystander CPR status were excluded due to small numbers (see note on table 1 for detailed information).

Four mutually exclusive outcomes were analysed. These were: 1) No pre-hospital ROSC sustained to ED or ROSC in ED (-ROSC to/in ED; n=10 177); 2) Pre-hospital ROSC sustained to ED or ROSC in ED – survival to 29 days (+ROSC to/in ED); n=3485); 3) survival to 30-364 days (Surv30-364days: n=113); and 4) survival to 365 days or more (Surv365days+: n=1367).

<u>Analyses</u>

Analyses were undertaken using SPSS software (IBM, Armonk, NY, USA). Descriptive analyses were completed by outcome (chi-square tests for categorical data, ANOVA for numerical data).

The variables initial rhythm and number QAS shocks were not included in any modelling due to redundancy to other variables (shockable and QAS shocks respectively).

Multinomial logistic regression was used to calculate odds ratios and 95% confidence intervals. The reference outcome for all modelling was -ROSC to/in ED. First, crude analyses were completed to identify variables independently associated with the outcome (unadjusted for any other variables). All variables that were significantly associated with one of the outcomes in crude (unadjusted) analyses were entered into a model. Variables that were not significantly associated with any of the outcomes in this new model were then removed from the model, one at a time, and the impact on the remaining variables was assessed. If the OR of the variables remaining in the model changed more than 10%, then the variable was retained in the model as a confounder (this included QAS shocks and response interval). Otherwise, the variable was excluded. Two variables were removed in this way (pre-QAS shocks and season). All other variables remained in the final adjusted model.

<u>Ethics approval</u>

Ethical approval for this study was obtained from Prince Charles Hospital Human Research Ethics Committee (approval number 15/QPCH/265), and from James Cook University Human Research Ethics Committee (approval number H5752). Access to confidential data was obtained via the Public Health Act through Queensland Health (approval number RD006708).

Results:

There were 15,142 cases that met inclusion criteria over the 13-year period of this study (2002-2014). Cases that did not receive a resuscitation attempt have been previously examined[8, 9].

Sample characteristics by outcome are displayed in Table 1. Crude risk factors of outcome are displayed in Table 2. Variables associated with outcomes following OHCA after adjusting for relevant confounders are shown in Table 3. Prior to 2007, intubation, LMA placement and adrenaline administration were not recorded in the QAS OHCA registry. Hence, crude and multivariate analyses (Tables 2&3) were restricted to data from 2007-2014 (n=9388).

Variables positively (and significantly) associated with survival to 365 days after adjusting for all relevant confounders are: an initial shockable rhythm; bystander witnessed events with bystander CPR; paramedic witnessed events; intubation placement; time of day (midday-2.59pm); and CCP attended scene.

Variables inversely (and significantly) associated with survival to 365 days after adjusting for all relevant confounders are: age (for every year of age, survival to 365 days+ reduces by 4%); geographical remoteness (specifically, outer regional areas); adrenaline administration; and time of day 9pm-11.59pm.

Discussion:

This study is the first to the authors' knowledge to use pre-hospital identified cases to build a predictive model for long-term outcomes (including 365 days+) of OHCA of cardiac aetiology. This study provides a larger sample and covers a broader time frame than previous similar studies[2-4] and explores geographical remoteness and SES, thus it is a novel addition to the current evidence base.

CCP Attendance

In this study, CCP attendance at an OHCA was associated with a 53% increase in survival to 365 days+. Previous evidence strongly suggests the extended skills of CCPs, such as intubation and some drug administration, are not the important factors to achieving good outcomes from OHCA[16-20]. Furthermore, the application of ALS involves additional risks such as oesophageal intubation, reduced chest compression fraction and delays to definitive management of the underlying disease. Therefore, recent focus has moved to the importance of high-quality CPR and early defibrillation[18, 21]. This has bought to question the requirement for CCPs at OHCA cases. One study showed that patients who received ALS (with advanced skills such as intubation and drug administration), had lower survival at hospital discharge, survival to 90 days and preferred neurological outcomes, than those receiving BLS only (limited skills such as BVM and automated defibrillators use)[22], although there were some major limitations, such as sample selection, lack of important clinical variables, and analyses completed[23]. In contrast, the findings of our study suggest that CCPs are valuable in achieving favourable outcomes from OHCA (survival to 365 days+) and provides an extra level of validation to the findings of a previous Queensland study, which reported a positive association between intensive care paramedic attendance at OHCA and survival to hospital discharge (AOR 1.43; 95%CI: 1.02-1.99)[15].

The importance of non-technical skills such as leadership and communication in emergency care have been increasingly recognised[23-25]. CCPs have more pre-hospital experience and a greater ongoing exposure to high acuity cases, such as OHCA, than ACPs. This experience and familiarity likely leads to the application of these non-technical skills and subsequently a more composed, structured, organised and efficient scene, which continue into the post arrest phase of care. Additionally, CCPs' knowledge of priorities and post resus care treatment options are more extensive. Collectively this is likely to result in better outcomes, as found by this study and suggested by another rigorously designed study showing improved outcomes with early advanced life support attendance[5]. This theory is also concurrent with findings from other out-of-hospital studies showing results in favour of a team-focused, coordinated approach[26-30].

Remoteness and socioeconomic status

In our study, there was inverse association between geographical remoteness and survival to 365 days+. Compared with major cities, odds of long-term survival were lower in people living in inner and outer regional areas, as well as remote/very remote areas. Odds were lowest in people living in outer regional areas, and this was the only association that was significant. This is consistent with expectations that preferred outcomes reduce as remoteness increases, due to longer response times and reduced access to health care[31, 32]. The QAS has been promoting remote specific strategies[11, 33], so it may be that these have been successful, yet focused, leading to a lack of improvement in the outer regional vs inner regional areas. This phenomenon was also suggested in a previously published study by the same authors using the same dataset in Queensland[10], where a stagnancy in trends over time of incidence of survival to 365 days+ were observed in inner and outer regional areas (females only), whereas rates increased in all other remoteness categories. However, it should be noted that this finding should be interpreted with caution due to sample size (especially in relation to cases in the remote/very remote areas). Further investigation is required.

In this study, there was no association between SES (as measured through SEIFA) and survival to 365 days+. These findings represent an important advancement relative to previous research, where inverse associations between SES and survival have been reported[34, 35]. However, these studies have focused on survival to 30 days, and inclusion of the linked data allowed this study to assess survival to 365 days+.

Length of Resuscitation

Length of resuscitation attempt is associated with survival from OHCA[6, 7]. However, this is not a variable in the QAS OHCA Registry and therefore could not be included for analyses in this study. This may explain several findings, related to the ALS procedure variables (intubation, LMA and adrenaline). A short resuscitation attempt usually occurs under 2 circumstances: 1) The attempt has been deemed futile shortly after commencement, so is ceased early - ALS procedures are less likely and the outcome is NROSC; or 2) ROSC has been achieved early – The earlier ROSC is achieved, the less chance that intra-arrest ALS procedures are undertaken and the more likely a better outcome. This likely explains the inverse associations observed in this study between adrenaline administration and all outcomes (compared with NROSC) and that this association became more pronounced as the outcome improved. Nevertheless, the use of intra-arrest adrenaline is a long-standing point of discussion. It may be that these results reflect a true negative impact from adrenaline use, as suggested in a previous study which did adjust for no and low flow times (length of resuscitation was excluded due to collinearity)[2]. Alternatively, these results may reflect a lack of effect, as strongly suggested by the recent PARAMEDIC 2 study[36].

Short resuscitation attempts due to futility (point 1 above) explains the positive association found between intubation and all outcomes (when compared with NROSC); and early success (point 2 above) explains the significantly greater association of intubation with survival to <30 days than survival to 365 days+. Placement of an LMA is the first line of ALS airway management in OHCA and can be undertaken by all paramedic levels in Queensland (intubation is a CCP only skill), so is undertaken more frequently and usually earlier than intubation. This likely explains the common lack of significant findings in all outcomes regardless of their reduced use in some short resuscitation attempts. A step-wise approach to airway management during OHCA is currently recommended[18], so advanced airway adjuncts are no longer a focus and are generally placed later in the resuscitation attempt. Additionally, a guideline was introduced by the QAS in 2013 whereby advanced procedures were undertaken only after six minutes of BLS[37], which delays advanced airway placement (LMA more so than intubation) and adrenaline administration further, and would most likely result in a more pronounced impact on the observed associations. Nevertheless, this would have only impacted up to the last two years of data included in this study.

The very low numbers observed in the outcome category survival to 30-364 days raises some interesting questions that require further exploration, regarding the most useful end point for long-term outcome. The low numbers in this category prevented meaningful comparison of predictors of this outcome and survival to 365 days+.

Strengths and Limitations

In this population-based study, data from 8 years (2007-2014) and 3 separate routinely collected administrative databases for the whole state of Queensland were linked to identify predictors of survival from OHCA, and of most novelty, survival to 365 days+. This facilitated investigation of previously under-explored variables (such as remoteness and SEIFA) and long-term survival. While this was a large data set, there is potential for type 1 error in some of the findings, particularly in relation to the outcome category survival to 30-364 days, and for some of the independent variables (people living in remote/very remote areas, and some of the clinical variables such as pre-QAS shocks, and witnessed events). Hence the findings should be interpreted with caution.

Alongside it's retrospective nature, this study has several other limitations. Firstly, there were important factors which could not be adjusted for, such as collapse to call interval, length of resuscitation, CPR quality (bystander and QAS) and experience of a previous OHCA event, which may have an impact on outcomes from OHCA. Additionally, there were changes in ILCOR guidelines (including less emphasis on ALS procedures and more emphasis on CPR quality and early defibrillation)[38] during the study period, new monitors/ defibrillators were introduced, paramedic education developed and there has been an increasing general focus on OHCA management in QAS[33, 39]. These factors all likely have a positive impact on survival. Secondly, the datasets used have limitations, such as differing levels of completeness and accuracy, with potentially differing coding practices over time. Thirdly, SES was measured using SEIFA, which is a broad measure applied by region (mapped from postcode), rather than individual (for example as measured through income). Fourthly, age was managed as a continuous variable, rather than as age-groups. Although this is preferable statistically, it means the impact of factors affecting specific age groups on survival, such as the chronic disease epidemic of middle age, would not be seen. Finally, there are confounders that could not be analysed in this study because they do not appear as variables in the routinely collected data that was linked for this study (e.g., variables such as smoking, alcohol consumption, underlying health conditions, access to and participation in rehabilitation, etc). Additionally, the number of paramedics on scene at the OHCA may be a confounding factor, but was unavailable for collection.

Conclusion:

This study shows that several factors are associated with survival from an OHCA to 365days+, including attendance of a CCP. From a service provision perspective, attendance of a CCP at an OHCA may be an important factor to achieve preferred long-term outcomes. Since factors other than the extended clinical skills of CCPs, such as their enhanced experience, exposure and expertise, are likely the primary cause, strategies which specifically optimise these should be investigated and implemented as soon as feasibly possible.

Community strategies promoting early recognition and access of emergency services should be continued and further developed, along with programmes to learn and maintain bystander CPR skills.

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Table 1. Sample characteristics – OHCA in Qld, Australia, by outcome

	-ROSC to/in ED n=10,177	+ROSC to/in ED n=3,485	Surv30-364days n=113	Surv365days+ n=1,367
Demographic variables				
Age (mean ±SD), years	70.3 ±13.7	69.6 ±13.7	70.1 ±14.3	62.01±13.4
Gender				
Female	3,144 (30.9%)	1,223 (35.1%)	33 (29.2%)	332 (24.3%)
Male	7,033 (69.1%)	2,262 (64.9%)	80 (70.8%)	1,035 (75.7%)
Remoteness (n=9 missing)				
Major City	6,004 (59.0%)	2,249 (64.6%)	63 (55.8%)	843 (61.7%)
Inner Regional	2,384 (23.4%)	688 (19.8%)	30 (26.5%)	313 (22.9%)
Outer Regional	1,578 (15.5%)	466 (13.4%)	19 (16.8%)	183 (13.4%)
Remote/Very Remote	205 (2.0%)	79 (2.3%)	1 (0.9%)	28 (2.0%)
SES (n=18 missing)				
(most advantaged) 9&10	1,424 (14.0%)	431 (12.4%)	9 (8.0%)	197 (14.4%)
7&8	3,081 (30.3%)	1,020 (29.3%)	39 (34.5%)	422 (30.9%)
5&6	1,932 (19.0%)	709 (20.4%)	26 (23.0%)	275 (20.1%)
3&4	1,863 (18.3%)	631 (18.1%)	19 (16.8%)	227 (16.6%)
(least advantaged) 1&2	1,863 (18.3%)	690 (19.8%)	20 (17.7%)	246 (18.0%)
Clinical variables				
††Initial rhythm (n=236 missing)				
VF	2,794 (27.7%)	1,516 (44.6%)	61 (58.1%)	1,038 (78.8%)
VT	46 (0.5%)	61 (1.8%)	10 (9.5%)	66 (5.0%)
PEA	2,163 (21.4%)	900 (26.5%)	17 (16.2%)	70 (5.3%)
Asystole	4,909 (48.7%)	804 (23.7%)	13 (12.4%)	85 (6.5%)
Other	175 (1.7%)	116 (3.4%)	4 (3.8%)	58 (4.4%)
Shockable (n=236 missing)				
Yes	2,840 (28.2%)	1,577 (46.4%)	71 (67.6%)	1,104 (83.8%)
No	7,247 (71.8%)	1,820 (53.6%)	34 (32.4%)	213 (16.2%)
Pre-QAS shocks				
Yes	54 (0.5%)	28 (0.8%)	1 (0.9%)	25 (1.8%)
No	10,123 (99.5%)	3,457 (99.2%)	112 (99.1%)	1,342 (98.2%)
††Number QAS shocks (mean ±SD) (n=945 missing)	1.9 ±3.0	2.3 ±3.1	1.8 ±2.3	2.1 ±2.2
QAS shocks (n=1 missing)				
Yes	4,913 (48.3%)	2,150 (61.7%)	81 (71.7%)	1,153 (84.3%
No	5,263 (51.7%)	1,335 (38.3%)	32 (28.3%)	214 (15.7%)
Witnessed arrest / bystander CPR (†††n=323 missing)				
Not wit, no CPR	2002 (20.1%)	407 (11.9%)	6 (5.5%)	47 (3.5%)
Not wit, CPR	2420 (24.3%)	489 (14.3%)	3 (2.8%)	73 (5.5%)
Bystander wit, no CPR	1588 (15.9%)	589 (17.2%)	16 (14.7%)	97 (7.3%)
Bystander wit, CPR	2977 (29.9%)	1207 (35.3%)	33 (30.3%)	483 (36.2%)
Paramedic wit	971 (9.8%)	724 (21.2%)	51 (46.8%)	636 (47.6%)
†Intubated (n=5249 missing)				
Yes	2535 (39.3%)	1427 (61.3%)	23 (25.6%)	264 (25.7%)
No	3,916 (60.7%	899 (38.7%)	67 (74.4%)	762 (74.3%)

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Table 1, continued

	-ROSC to/in ED n=10,177	+ROSC to/in ED n=3,485	Surv30-364days n=113	Surv365days+ n=1,367
†LMA (n=5249 missing)				
Yes	2,041 (31.6%)	647 (27.8%)	12 (13.3%)	163 (15.9%)
No	4,410 (68.4%)	1,679 (72.2%)	78 (86.7%)	863 (84.1%)
†Adrenaline (n=5249 missing)				
Yes	5,027 (77.9%)	1,857 (79.8%)	30 (33.3%)	292 (28.5%)
No	1,424 (22.1%)	469 (20.2%)	60 (66.7%)	734 (71.5%)
Event based variables				
Time of day (n=191 missing)				
Midnight-5.59am	1,523 (15.2%)	446 (13.0%)	19 (16.8%)	172 (12.7%)
6am-8.59am	1,740 (17.3%)	504 (14.6%)	16 (14.2%)	212 (15.7%)
9am-11.59am	1,524 (15.2%)	557 (16.2%)	26 (23.0%)	289 (21.4%)
Midday-2.59pm	1,263 (12.6%)	563 (16.4%)	7 (6.2%)	270 (20.0%)
3pm-5.59pm	1,541 (15,3%)	551 (16.0%)	17 (15.0%)	204 (15.1%)
6pm-8.59pm	1,394 (13.9%)	456 (13.2%)	16 (14.2%)	152 (11.2%)
9pm-11.59pm	1,057 (10.5%)	366 (10.6%)	12 (10.6%)	54 (4.0%)
Day of week				
Sunday	1,442 (14.2%)	522 (15.0%)	20 (17.7%)	191 (14.0%)
Monday	1,539 (15.1%)	497 (14.3%)	17 (15.0%	194 (14.2%)
Tuesday	1,417 (13.9%)	499 (14.3%)	19 (16.8%)	195 (14.3%)
Wednesday	1,463 (14.4%)	472 (13.5%)	12 (10.6%)	183 (13.4%)
Thursday	1,390 (13.7%)	477 (13.7%)	18 (15.9%)	189 (13.8%)
Friday	1,471 (14.5%)	528 (15.2%)	12 (10.6%)	200 (14.6%)
Saturday	1,455 (14.3%)	490 (14.1%)	15 (13.3%)	215 (15.7%)
Season				
Summer	2,227 (21.9%)	799 922.9%)	27 (23.9%)	336 (24.6%)
Autumn	2,427 (23.8%)	877 (25.2%)	27 (23.9%)	320 (23.4%)
Winter	3,048 (29.9%)	984 (28.2%)	28 (24.8%)	361 (26.4%)
Spring	2,475 924.3%)	825 (23.7%)	31 (27.4%)	350 (25.6%)
System based variables				
CCP attended				
Yes	6,437 (63.3%)	2,473 (71.0%)	70 (61.9%)	858 (62.8%)
No	3,740 (36.7%)	1,012 (29.0%)	43 (38.1%)	509 (37.2%)
Response interval (mean ±SD), mins (n=404 missing)	11.0 ±38.2	9.2 ±15.2	10.6 ±16.5	9.3 ±9.7

-ROSC to/in ED = No pre-hospital ROSC sustained to ED or ROSC in ED; +ROSC to/in ED = Pre-hospital ROSC sustained to ED or ROSC in ED; Surv30-364days = Survival to 30-364 days; Surv365days+ = Survival to 365 days or more

†Prior to 2007, intubation, LMA and adrenaline administration were not recorded in the QAS OHCA registry, so the numbers presented relate only to 2007-2014

††No further analyses were undertaken on these variables due to redundancy

†††This category is made up of the following cases: 13 unknown witnessed, unknown CPR; 77 bystander witnessed, unknown CPR; 69 not witnessed, unknown CPR; 91 unknown wit, CPR; 73 unknown wit, no CPR

35 patients experienced 2 OHCA events and 1 patient experienced 3 OHCA events, during the study time period

Table 2. Crude risk factors of outcome (OR and 95%CI)

	+ROSC to/in ED	Surv30-364days	Surv365days+
Demographic variables			
Age, years	**0.994 (0.991-0.997)**	0.998 (0.982-1.013)	**0.954 (0.949-0.959)**
Gender			
Female	-	-	-
Male	**0.83 (0.75-0.92)**	1.02 (0.65-1.595)	**1.497 (1.28-1.75)**
Remoteness			
Major City	-	-	-
Inner Regional	**0.86 (0.76-0.96)**	1.31 (0.82-2.11)	0.94 (0.799-1.10)
Outer Regional	**0.80 (0.697-0.92)**	0.89 (0.47-1.68)	**0.78 (0.63-0.95)**
Remote+	1.08 (0.77-1.50)	0.61 (0.08-4.45)	1.12 (0.71-1.76)
SES			
9&10	-	-	-
7&8	1.06 (0.91-1.25)	**2.47 (1.03-5.92)**	0.94 (0.76-1.16)
5&6	**1.199 (1.01-1.42)**	**2.54 (1.02-6.33)**	1.06 (0.85-1.33)
3&4	1.06 (0.89-1.26)	1.48 (0.56-3.97)	0.81 (0.64-1.03)
1&2	1.13 (0.95-1.34)	2.20 (0.87-5.57)	0.91 (0.72-1.15)
Clinical variables			
Shockable			
No	-	-	-
Yes	**2.35 (2.13-2.60)**	**5.896 (3.72-9.34)**	**15.44 (12.92-18.44)**
Pre-QAS shocks			
No	-	-	-
Yes	1.32 (0.78-2.26)	1.72 (0.23-12.595)	**2.42 (1.35-4.32)**
QAS shocks			
No	-	-	-
Yes	**1.57 (1.43-1.73)**	**2.44 (1.55-3.84)**	**5.58 (4.68-6.64)**
Witnessed arrest / bystander CPR			
Not wit, no CPR	-	-	-
Not wit, CPR	0.92 (0.78-1.099)	0.24 (0.05-1.17)	1.07 (0.71-1.61)
Bystander wit, no CPR	**1.81 (1.51-2.18)**	**3.32 (1.26-8.76)**	**1.96 (1.28-3.01)**
Bystander wit, CPR	**2.01 (1.72-2.35)**	**2.595 (1.05-6.39)**	**6.58 (4.69-9.22)**
Paramedic wit	**3.43 (2.88-4.09)**	**13.07 (5.53-30.90)**	**22.59 (16.08-31.74)**
Intubated			
No	-	-	-
Yes	2.45 (2.23-2.70)	**0.53 (0.33-0.85)**	**0.54 (0.46-0.62)**
LMA			
No	-	-	-
Yes	**0.83 (0.75-0.93)**	**0.33 (0.18-0.61)**	**0.41 (0.34-0.49)**
Adrenaline			
No	-	-	-
Yes	1.12 (0.998-1.26)	**0.14 (0.09-0.22)**	**0.11 (0.10-0.13)**

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Table 2, continued

	+ROSC to/in ED	Surv30-364days	Surv365days+
Event based variables			
Time of day			
Midnight-5.59am	-	-	-
6am-8.59am	0.93 (0.78-1.10)	0.51 (0.24-1.08)	1.06 (0.83-1.36)
9am-11.59am	1.17 (0.99-1.396)	0.96 (0.50-1.84)	**1.71 (1.36-2.16)**
Midday-2.59pm	**1.42 (1.19-1.69)**	**0.39 (0.15-0.97)**	**1.90 (1.49-2.41)**
3pm-5.59pm	1.17 (0.98-1.395)	0.69 (0.33-1.42)	**1.32 (1.03-1.69)**
6pm-8.59pm	1.05 (0.88-1.26)	0.76 (0.37-1.55)	1.01 (0.78-1.32)
9pm-11.59pm	**1.26 (1.04-1.52)**	0.86 (0.41-1.81)	**0.46 (0.32-0.66)**
Season			
Summer	-	-	-
Autumn	0.99 (0.87-1.14)	0.97 (0.52-1.79)	0.87 (0.72-1.06)
Winter	**0.85 (0.75-0.97)**	0.87 (0.48-1.58)	**0.77 (0.64-0.92)**
Spring	0.89 (0.78-1.02)	1.15 (0.64-2.09)	0.97 (0.81-1.17)
System based variables			
CCP attended			
No	-	-	-
Yes	**1.65 (1.48-1.85)**	0.696 (0.45-1.07)	**0.85 (0.74-0.98)**
Response interval, mins	0.997 (0.99-1.00)	1.00 (0.995-1.01)	0.995 (0.99-1.00)

+ROSC to/in ED = Pre-hospital ROSC sustained to ED or ROSC in ED; Surv30-364days = Survival to 30-364 days; Surv365days+ = Survival to 365 days or more
This model includes cases from 2007-2013 only (n=9388 valid cases); prior to 2007, intubation, LMA and adrenaline administration were not recorded in the QAS OHCA registry
Only variables that were significant in crude analysis are presented in this table
Statistically significant associations are shown in bold text

Table 3. Independent predictors of outcomes from OHCA in Qld, Australia (adjusted OR and 95%CI)

	Surv<30days	**Surv30-364days**	**Surv365days+**
Demographic variables			
Age	0.996 (0.992-1.00)	0.996 (0.98-1.01)	**0.96 (0.95-0.96)**
Gender			
Male	-	-	-
Female	**1.40 (1.25-1.57)**	1.19 (0.72-1.99)	0.99 (0.80-1.22)
Remoteness			
Major City	-	-	-
Inner Regional	0.87 (0.76-1.01)	1.03 (0.57-1.87)	0.79 (0.62-1.01)
Outer Regional	0.87 (0.74-1.02)	0.87 (0.42-1.80)	**0.62 (0.46-0.83)**
Remote/Very Remote	1.22 (0.84-1.78)	0.67 (0.09-5.20)	0.69 (0.36-1.31)
SES			
(most advantaged) 9&10	-	-	-
7&8	1.17(0.98-1.39)	**3.09 (1.17-8.13)**	1.11 (0.82-1.49)
5&6	**1.42 (1.17-1.72)**	2.45 (0.86-6.97)	1.07 (0.76-1.49)
3&4	**1.27 (1.05-1.55)**	1.35 (0.43-4.22)	0.99 (0.70-1.40)
(least advantaged)1&2	**1.38 (1.13-1.69)**	2.32 (0.78-6.91)	1.02 (0.72-1.45)
Clinical variables			
Shockable			
No	-	-	-
Yes	**2.39 (2.06-2.76)**	**5.73 (2.995-10.97)**	**11.97 (8.97-15.96)**
Witnessed arrest / bystander CPR			
Not wit, no CPR	-	-	-
Not wit, CPR	0.84 (0.70-1.01)	0.00 (0.00-0.00)	0.95 (0.59-1.51)
Bystander wit, no CPR	**1.57 (1.30-1.91)**	**3.05 (1.06-8.81)**	1.39 (0.84-2.29)
Bystander wit, CPR	**1.45 (1.23-1.71)**	1.88 (0.69-5.15)	**3.36 (2.25-5.02)**
Paramedic wit	**3.56 (2.95-4.30)**	**10.06 (3.87-26.14)**	**13.64 (9.07-20.51)**
Intubated			
No	-	-	-
Yes	**3.13 (2.71-3.62)**	1.47 (0.74-2.89)	**1.41 (1.10-1.81)**
LMA			
No	-	-	-
Yes	1.13 (1.00-1.28)	0.63 (0.31-1.28)	0.91 (0.72-1.15)
Adrenaline			
No	-	-	-
Yes	**0.74 (0.63-0.87)**	**0.16 (0.09-0.29)**	**0.07 (0.05-0.09)**

Table continues over page

Table 3, continued

	Surv<30days	Surv30-364days	Surv365days+
Event based variables			
Time of day			
Midnight-5.59am	-	-	-
6am-8.59am	0.93 (0.78-1.14)	0.63 (0.28-1.42)	1.28 (0.91-1.79)
9am-11.59am	1.16 (0.96-1.41)	1.01 (0.49-2.10)	**1.73 (1.25-2.40)**
Midday-2.59pm	**1.42 (1.17-1.73)**	0.42 (0.15-1.19)	**2.19 (1.57-3.07)**
3pm-5.59pm	1.13 (0.93-1.37)	0.89 (0.41-1.94)	1.35 (0.95-1.90)
6pm-8.59pm	0.98 (0.80-1.19)	0.67 (0.30-1.54)	1.03 (0.72-1.48)
9pm-11.59pm	1.18 (0.96-1.46)	0.58 (0.25-1.37)	**0.22 (0.14-0.36)**
System based variables			
CCP attended			
No	-	-	-
Yes	0.88 (0.74-1.04)	1.46 (0.81-2.61)	**1.53 (1.20-1.95)**

+ROSC to/in ED = Pre-hospital ROSC sustained to ED or ROSC in ED; Surv30-364days = Survival to 30-364 days; Surv365days+ = Survival to 365 days or more
This model includes cases from 2007-2014 only (n=9388 valid cases); prior to 2007, intubation, LMA and adrenaline administration were not recorded in the QAS OHCA registry
Analyses adjusted for the following confounders: QAS Shocks; response Interval
Statistically significant associations are shown in bold text

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7.3 Chapter Summary

- This is the first study known to the authors to undertake multivariate analyses to predict outcomes from OHCA in Australasia.
- Multinomial logistic regression was used to calculate odds ratios and 95% confidence intervals associated with outcomes from OHCA.
- Variables positively (and significantly) associated with survival to 365 days after adjusting for all relevant confounders are: an initial shockable rhythm; bystander witnessed events with bystander CPR; paramedic witnessed events; intubation placement; time of day (midday-2.59pm); and CCP (Critical Care Paramedic) attended scene.
- CCP attendance at an OHCA was associated with a 53% increase in survival to 365 days+. This is likely due to their enhanced experience, exposure and expertise to that of an ACP and the consequent better application of non-technical skills.
- Variables inversely (and significantly) associated with survival to 365 days+ after adjusting for all relevant confounders are: age (for every year of age, surv365 days+ reduces by 4%); geographical remoteness (specifically, outer regional areas); adrenaline administration; and time of day 9pm-11.59pm.

7.4 Final Word (Chapter 7)

This Chapter comprises the final publication in the thesis and was designed to investigate pre-hospital predictors of adult OHCA of presumed cardiac aetiology in Queensland, Australia. It is a novel addition to the literature and provides essential information for service provision. This Chapter address the third and final aim (*To investigate predictors of survival from OHCA)* of the thesis. The following Chapter (Chapter 8) presents a discussion and synthesis of the findings from each publication presented in the thesis, in the context of relevant literature, and the strengths and limitations of the overall programme of research.

Chapter 8: Discussion and Conclusion

8.1 Overview

In this Chapter, the findings of the overall programme of work described in the thesis are summarised by the three thesis aims, in the context of relevant literature, strengths and limitations of the work, and implications for policy, practice and research. This Chapter culminates in an overall conclusion.

8.2 Discussion

In this thesis, the findings of a series of studies that were conducted to inform future policy and practice in the management of adult OHCA of cardiac aetiology in high-income countries with well-developed health care services were presented. The primary focus of this thesis is the management of OHCA in the pre-hospital phase, however some findings are likely transferable to inform management of the in-hospital phases and beyond.

This research was undertaken in a sequential approach with each study complementing the previous by providing novel, progressive and meaningful additions to the evidence base. Additionally, to ensure that the findings of this study would be relevant and useful to industry, through specific consultation, each phase was a development on previous/concurrent QAS-specific work in this field[1-4] and in-line with QAS requirements and the QAS strategic plan[5].

This thesis had 3 aims:

1) To explore current literature in relation to resuscitation strategies that could be used by paramedics in a pre-hospital setting to improve outcomes from OHCA
2) To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia
3) To investigate predictors of survival from OHCA

Each aim of this research was addressed by one or more sub-studies. This included a systematic search and review of literature to identify strategies that paramedics could use to improve outcomes from adult OHCA (Chapter 2, publications 1 and 2, aim 1); epidemiological analyses and temporal trends of the incidence of pre-hospital outcomes from adult OHCA of presumed cardiac aetiology in Queensland, Australia (Chapters 4 and 5, publications 3 & 4, aim 2); epidemiological analyses and temporal trends of the incidence of long-term outcomes from adult OHCA of presumed cardiac aetiology in Queensland, Australia (Chapter 6, publication 5, aim 2); and a study to identify independent pre-hospital predictors of adult OHCA (Chapter 7, publication 6, aim 3). Figure A illustrates the aims, Chapters and publications in a conceptual model of this thesis.

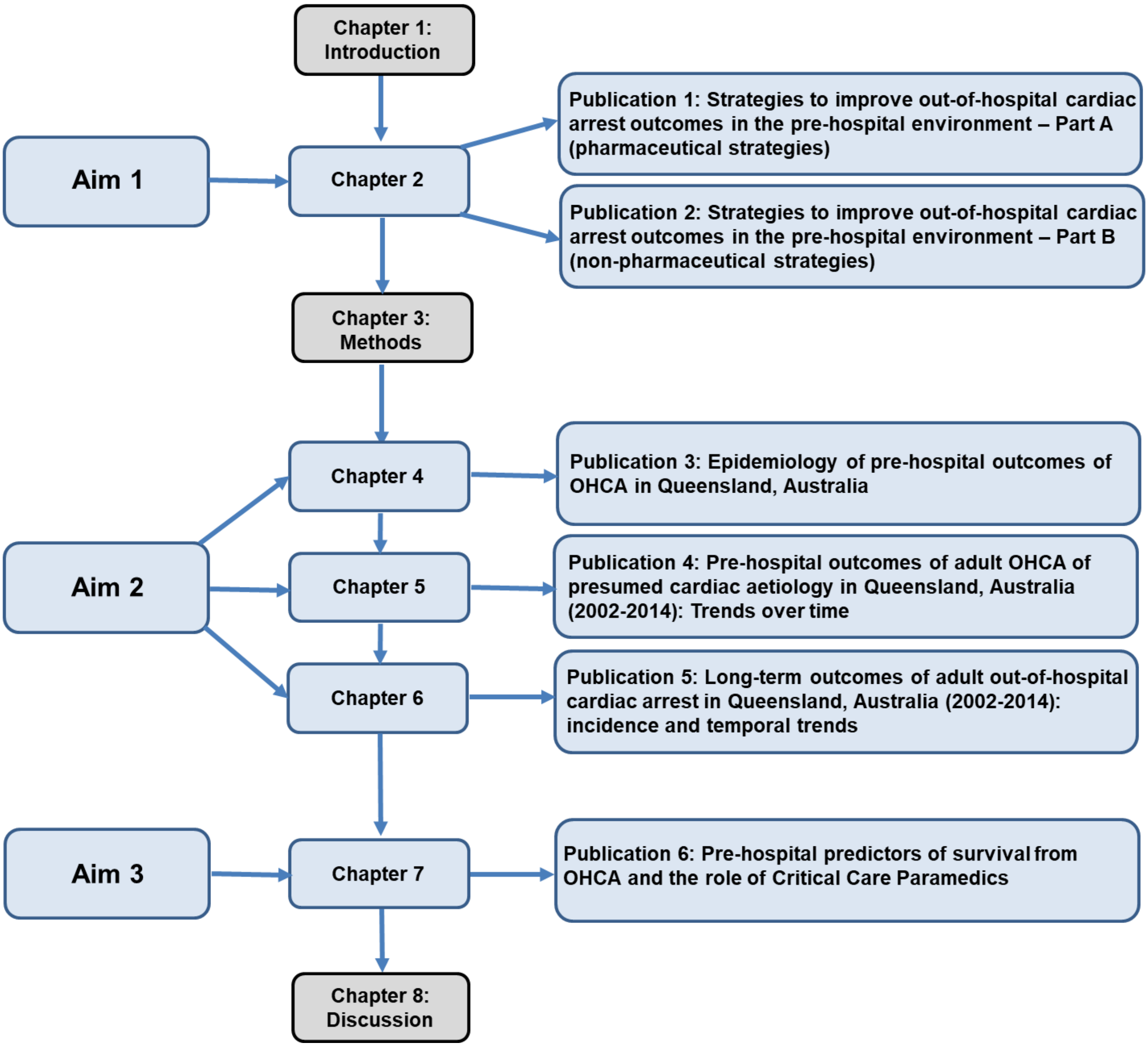

Figure A: Conceptual model of thesis

Aim 1: To explore current literature in relation to resuscitation strategies in a pre-hospital setting to improve outcomes from OHCA

A systematic search and review of recent literature was conducted to address aim 1 of this thesis. This was undertaken to identify strategies which could be used by paramedics in the pre-hospital environment to improve outcomes from adult OHCA of presumed cardiac aetiology, to describe and synthesise the evidence, and to make recommendations for the future. Twenty-eight separate studies were identified for full review, that were considered in six separate groups of strategies. These were: use of a modified resuscitation protocol (primarily aimed at improving CPR quality); use of a mechanical chest compression device; intra-thoracic pressure regulation; vasopressin administration; thrombolysis administration; and application of therapeutic hypothermia. The results of this systematic search and review are presented in Chapter 2 of this thesis, over two publications: Part A presenting pharmaceutical strategies (Publication 1) and Part B presenting non-pharmaceutical strategies (Publication 2).

Overall, there was a lack of high-quality, methodologically rigorous research identified in this review. This is likely a true reflection of the state of research in this field, as the search criteria were broad and encapsulated many studies, so inadequate inclusion criteria or search methods are an unlikely explanation. Upon reflection, the lack of published methodologically rigorous literature is unsurprising, as it is only in relatively recent times that higher rates of preferable outcomes from OHCA have been reported, which sparked an increase of studies in this area. Most likely the quality of studies will improve over time. Therefore, a primary recommendation from the systematic search and review is the undertaking of more high-quality, methodologically rigorous studies that assess innovative strategies to improve outcomes form OHCA.

Use of a modified resuscitation protocol to improve the quality of CPR (preferably alongside a pit crew approach) was the only strategy with evidence sufficient to warrant a recommendation for immediate implementation where feasible. This is concurrent with the current climate, where high-quality CPR and early defibrillation are the focus in the management of non-traumatic cardiac arrest[6-12], combined with an increased recognition of optimising the efficiency of teams[13-15]. In fact, use of a modified resuscitation protocol alongside a pit-crew approach, combines those factors so if broadly implemented could be the next step to significantly improving OHCA outcomes.

The mechanical chest compression device currently shows no clear benefit in the routine management of OHCA. Evidence suggests that it provides CPR in line with good quality manual CPR, and there are clear practical advantages in its use, so these must be considered. For example, for use in cases such as prolonged resuscitation attempts and those requiring transport to more definitive care, such as interventional cardiology and/or extracorporeal membrane oxygenation (ECMO). Consequently, a recommendation from this review is to introduce the use of a mechanical chest compression device where clear practical advantages and feasibility exist. This is in-line with ILCOR recommendations[16] and European Resuscitation Council guidelines[17]. Further research should focus on the subsets of patients where the practical advantages exist, such as those requiring transport. Additionally, further circumstances should be considered. For example, practical advantages may exist in some cases where a single-person response only is available. This would facilitate defibrillation without pausing chest compressions and avoid CPR provider fatigue, usually managed by rotating the provider every two minutes. There may be detrimental effects to this approach such as reduced CPR fraction (proportion of time (%) chest compressions are performed during a cardiac arrest) while the device is being applied; the risk-benefit offset is currently unknown, so is an area requiring exploration.

This review identified studies using two types of mechanical chest compression device, the Autopulse and LUCAS (I & II). There are other device types available such as Corpuls CPR, Lifeline (manufactured by Defibtech) and Thumper (manufactured by Michigan Instruments), all of which have a pneumatic piston design. Little recent published research and none on humans, was identified on these other device types. Studies used either swine[18-20] or manikins[21] and although promising results in-line with Autopulse and LUCAS were demonstrated, these devices should not be implemented until good quality human-based studies have been undertaken.

Where used, it is essential that mechanical chest compression devices are used by staff who have received specific training to ensure the devices are properly positioned, functioning correctly and interruptions in compressions are minimised and preferably avoided in situations such as initiation, repositioning or device insufficiency or failure. An ED based study showed that set up times can be reduced with use of a pit crew approach to resuscitation[22]. This finding is likely transferable to the pre-hospital field, so alongside the primary recommendation of this review (immediate implementation of a modified resuscitation protocol, preferably with some kind of pit crew approach), this seems like the safest and most efficient method for implementation.

The remaining strategies (pharmaceutical and non-pharmaceutical) showed no strong evidence to support their immediate implementation in routine management of OHCA.

The three included studies of intra-thoracic pressure regulation all had inherent flaws[23-25], so interpretability was limited. Nevertheless, there are indications of benefit, so high-quality independent studies of this strategy are recommended. This strategy is intended to enhance circulation, but this cannot be achieved without high quality CPR. In some cases, intrathoracic pressure regulation has been investigated together with other strategies[23, 24, 26] intended to improve CPR quality, such as active compression/decompression CPR. In order to distinguish benefit of intrathoracic pressure regulation alone and/or the synergistic effect of other strategies, it is essential that studies have CPR quality assurance processes in place in both intervention and non-intervention groups. Further studies should also aim to capture advances in the technology of intrathoracic pressure regulation, such as CirQlator [27], the current studies for which did not meet the study design inclusion criteria for this review.

Therapeutic hypothermia was the final non-pharmaceutical strategy identified in the review. Although this strategy has routinely been used in the post-arrest patient in-hospital for some time, the current evidence does not support its use in pre-hospital settings. Recent high quality in-hospital studies have suggested that the benefit comes from preventing hyperthermia, rather than establishing hypothermia[28]. With this in mind, since the natural onset of hyperthermia in the post-arrest patient is not instantaneous, but comes on in the hours following the event, the finding that pre-hospital induction of hypothermia (and the consequent prevention of hyperthermia) provides no benefit over in-hospital induction, is unsurprising. This phenomenon needs to be considered in future study design, along with the preferred timing (intra-arrest v. post-arrest) and method of application, which were not consistent across studies. Additionally, evidence surrounding other methods of therapeutic hypothermia application, such as Rhinochill, requires development and monitoring. Rhinochill is an intra-nasal cooling device, for which neither of the two studies examining this device [29, 30] employed a study design with enough rigour to be included in this review.

Neither pharmaceutical strategy (vasopressin or thrombolysis administration) showed strong supportive evidence for use in the intra-arrest phase of adult OHCA. Administration of these drugs for this purpose has been researched for some time, showing no high-quality evidence for their benefit. It may be that they have benefit in specific patient subsets which are yet to be investigated. It may also be that a lack of rigour in the studies is responsible for the lack of effect found. Therefore, it is recommended that more rigorous, patient specific studies are undertaken, and the evidence base is monitored.

This systematic search and review did have limitations which need to be considered when interpreting the findings. In addition to the six strategy groups the included articles were separated into, there were six further strategies that were excluded from the review as only one study was identified in which that strategy was examined. These were passive oxygen insufflation; hypertonic saline administration; erythropoietin administration; lignocaine administration prophylactically; procainamide administration; and waveform analysis-guided shock timing. These six strategies (and potentially others not identified in the review) cannot be excluded from having potential benefit. The evidence base should be monitored and reassessed accordingly. Other limitations include that articles not written in English or that were published in grey literature were not considered. Finally, this review was not a systematic review. While systematic methods were used to obtain all relevant literature and reference was made to the quality and rigour of included studies, detailed critical appraisal of each included paper was not conducted. The objective of the review was intentionally broad, and a number of relevant strategies were identified in the studies yielded by the search criteria, making critical appraisal impractical and not feasible.

Aim 2: To explore epidemiology and temporal trends (2002-2014) of OHCA in Queensland, Australia

Aim 2 of this thesis is addressed in Chapters 4, 5 and 6 (Publications 3, 4 and 5). This programme of work is the first where incidence of OHCA stratified by outcome has been examined in Australasia. Additionally, this is the first study internationally where outcomes from adult OHCA of cardiac aetiology have been reported at this level of detail using such rigorous methodology. Data linkage was used to combine three large reputable datasets (see Chapter 3) to calculate and analyse epidemiology and temporal trends in incidence of pre-hospital (Chapter 4, publication 3; Chapter 5, publication 4) and long-term outcomes (including survival to 365 days+) (Chapter 6, publication 5) from OHCA over a 13-year period (2002-2014). Incidence rates and temporal trends were calculated for total OHCA events, and separately by outcome, then stratified by age, gender, geographical remoteness and socio-economic status.

Population-based incidence (per 100,000 persons) was the measure used throughout these Chapters, as it accounts for changes in demographics at the population level so better informs the true burden on public health than other measures.

The findings related to aim 2 of this thesis are summarised below, within separate sub-sections (age, gender, geographical remoteness, socio-economic status and temporal trends - overall, and within these characteristics).

Age/gender

The work presented in this thesis indicates a crude incidence (per 100,000 persons) of total adult OHCA events at 73.95 (95%CI: 73.12-74.78) – slightly lower for females (50.32; 95%CI: 49.36-51.28), and higher for males (98.14; 95%CI: 96.78-99.49). Incidence rates calculated for this thesis are consistent with the few previous studies in which incidence from adult OHCA have been reported[4, 31-33]. Notably however, most of these previous studies have not reported incidence by outcome. An exception is the EuReCa study[34], which reported incidence of OHCA by resuscitation attempt, ROSC and survival for each European country that was in the study, from a sample encapsulating 1-month. In this thesis, publications 3-5 collectively report incidence of total OHCA events and by pre-hospital and long-term outcome including survival to 365 days+, over the duration of the study period (resulting in average incidence per annum), and separately for each calendar year over the 13-year timeframe of the study, allowing analyses of trends over time. Consequently, this programme of research facilitated a greater understanding of OHCA risk and outcome than previously reported, thereby addressing a substantial gap in the evidence base and providing an important and novel addition to the literature.

When stratified by gender, crude and age-standardised rates of OHCA overall and by outcome were typically twice as high in males as they were in females. This is consistent with rates reported in comparable regions (such as Victoria, Australia[35]) which show an approx. 2:1 ratio of OHCA events in males and females[33, 35-37] . This pattern was also observed generally in all age-groups in this study. Also concurrent with previous findings[4, 31] is that incidence of total OHCA events and each outcome increased with age for both genders.

Incidence rates and temporal trends of total OHCA events by age/gender:

Between 2002-2014, crude rates of total OHCA events increased significantly in males and females. Age & gender adjusted OHCA event rates (see Chapter 6, additional analyses) did not change over time. These findings are consistent with OHCA event rates observed in a similar study that was conducted in Perth, Western Australia over an earlier timeframe (1997-2010)[31], where stable age-gender-standardised incidence rates were observed from 2002 onwards, although OHCA event rates declined over the whole time period.

Interestingly, the findings reported in this thesis contradict a previous study that was conducted in Queensland over the same time period, in which no significant change over time in crude rates of OHCA events in males or females were observed[4]. In addition, age-standardised rates in males were observed in the previous study (no change in females)[4]. Although the same primary data source was used in both studies (QAS OHCA Registry), the final samples in the two studies differed slightly, as there were slight differences in methodology between the two studies. In the previous study, data from the QAS OHCA Registry were not linked with QHAPDC or RG Death Registry, so it relied solely upon the QAS OHCA Registry for information about age and aetiology, whereas in the current study reported in this thesis, cases with unknown age/aetiology were initially included and only excluded if age/aetiology remained unknown after linkage. Data linkage also identified some inaccurate ages and duplicate cases recorded within the QAS OHCA Registry, which led to some minor alterations to data and exclusion of cases. Additionally, data linkage allowed a more complete and accurate capture of residential postcode which enabled exclusion of 1735 non-Queensland residents for incidence rate calculations in this study compared with the previous study. Hence this is the most likely reason for the differences between the two data sets and therefore contradictory results in the two studies. Collectively, these factors led to differing samples in both accuracy and size between the study reported in this thesis and the previous Queensland study (30,560 and 32,346 respectively). There were also some minor differences between the two studies in the population data used, due to some updates by ABS since the first study was published. Finally, different software was used to calculate trends over time in each of the studies (Epi-info in the first study and STATA in the second study), which may have had an effect. Overall, the differences in methodology between studies explain the differing results. The methodology of the study presented in this thesis is more rigorous than the first study and consequently these results provide a more accurate reflection of reality.

Increasing age is a known risk factor for cardiovascular disease and cardiac arrest[4, 31, 38, 39]. Age brings a naturally deteriorating physical state, a prolonged period of exposure and subsequently an increased risk of developing chronic disease and cardiac arrest. Therefore, the observed increase in crude incidence rates of total OHCA events for both males and females, alongside the lack of significant change in rates after adjusting for age and gender, likely reflect the ageing population profile of Queensland[40]. This is an ongoing phenomenon which is predicted to intensify in Queensland and Australia in the coming years and brings challenges and changes for health care requirements and focus[41]. Consequently, in the OHCA field, a greater focus on the management of non-shockable rhythms and end of life care will likely be required[4].

In this thesis, the observed increased incidence of total OHCA events over time is more pronounced in the middle age years (45-64 years), which likely reflects the higher exposure to risk factors of chronic disease in these years and the resultant chronic disease epidemic[38, 42-44]. There is also evidence of a chronic disease epidemic in a previous Queensland study, in which stagnating incidence rates in the 65-69 year age-group were observed, alongside decreasing rates in most other age-groups[4]. The chronic disease epidemic also likely explains (at least partially) the lack of reduction in age and gender adjusted rates of OHCA events, despite the increasing focus on health and well-being, the developments in cardiac care and implementation of prevention strategies for cardiac arrest over the time of this study. This includes increased public education on person controllable risk factors such as a sedentary lifestyle, hypertension, smoking, poor diet and better access to assistance to improve these; more evidence-based cardiac medication; lower thresholds to undertake investigative procedures; and better rehabilitation facilities and access. Additionally, pre-hospital instigated reperfusion programmes, including pre-hospital fibrinolysis and pPCI referral have become well-established pathways of care in recent years in developed ambulance services, including QAS[45].

In the previous study conducted in Queensland[4] a more pronounced increase in total OHCA events was observed over time (2002-2014) in females in the 50-64 years age group than in other age groups, or than males in the same age group. Slightly different age groups were used in the study reported in this thesis, but in those age-groups encapsulating the 50-64 years group (45-54 and 55-64 years), rates increased over time for males and females, and as observed in the previous QLD study, this effect was more pronounced in females than males. This is an interesting finding and suggests the impact of the chronic disease epidemic and/or associated lifestyle risk factors on OHCA risk may be impacting females to a greater extent than males. As male gender is a known risk factor for cardiac disease and OHCA[38, 39], prevention strategies for OHCA have historically been targeted towards males or have been non-gender specific, despite that cardiovascular disease is a leading cause of illness and death amongst Australian women[46]. Future strategies should have a greater emphasis on females, which requires further investigation.

Temporal trends by age, gender and outcome:

This programme of work shows strong evidence that positive outcomes from OHCA are improving. Increases in incidence of the most preferred pre-hospital and long-term outcomes (Sustained-ROSC and Survival to 365 days+, respectively) were consistently observed over the study period for crude, gender-specific and all adjusted rates (age+gender, remoteness+gender and SES+gender). Incidence of survival to 365 days+ is the longest-term measure reported in the literature. Consequently, these results provide a level of certainty that outcomes are improving at a population level that has not been ascertained previously.

Multiple systems working synchronously are required to improve patient outcomes, so this finding is likely the result of improvements in care throughout the OHCA patient pathway, including pre-hospital, ED, ICU and rehabilitation services. Nevertheless, the specific increase in preferred pre-hospital outcomes observed over the study period in this thesis suggests that improvements in pre-hospital care have made a significant contribution. This is likely to be due to increasing preferred outcomes in some small population pockets internationally brought focus to this field which led to a substantial increase in the volume of research and subsequent evidence in this area. This resulted in changes to ILCOR recommendations in 2005 and 2010[47-50], which were included in Australian Resuscitation Council guidelines and adopted by QAS. These included an increased focus on high quality CPR with a change in compression to ventilation ratio in 2005 (from 15:2 to 30:2), along with a more patient-specific approach to care. Secondly, over the time period of this study the level of paramedic education has increased. Paramedics have recently (December 2018) become registered professionals and although this post-dated the data collection period of this study, there have been changes ongoing for some time in preparation. These include more contemporary training methods and equipment, four days a year rostered in-service training for all paramedics employed by QAS and an expectation of self-instigated continued professional development activities (now compulsory under registration).

Thirdly, QAS now only employs tertiary level trained paramedics. This extra level of education provides a more in-depth knowledge on condition pathologies and preferred treatments with a greater emphasis on evidence informed practice, giving paramedics the skills to provide a more holistic, patient-specific approach to care.

QAS have become more focused on OHCA management, including development of an OHCA focus group to develop and oversee clinical activity to improve outcomes, development of the OHCA initiative[1] and annual reporting on OHCA[3]. This has been supplemented with the instigation by QAS of various community-based initiatives such as the CPR Awareness scheme and delivering public education at events and in schools. Other community-based initiatives have also been instigated such as education through the Heart Foundation and other agencies such as St John’s and Australian Red Cross, public access defibrillator projects and mobile phone applications to assist with CPR and/or to identify and alert CPR providers nearby, such as GoodSAM[51].

In older year age groups, there was improvement in incidence of OHCA events resulting in Sustained-ROSC but not Survival to 365 days+, which could be a reflection that the younger aged groups respond better to in-hospital management and procedures such as PCI.

Increased research, changes in guidelines, increased education levels and ambulance service and paramedic focus on OHCA management collectively possibly explain the observed increase over time in crude, gender-specific and adjusted incidence of OHCA resulting in no-resuscitation. An increase in the rate of events resulting in no resuscitation may on the surface appear to be a negative finding, as it is the worst outcome. However, combined with the observed decrease over time in incidence of events resulting in no ROSC, and a dual increase in incidence of events resulting in sustained ROSC, and survival to 365 days+, suggests that there have been improvements in applied decision-making around resuscitation guidelines. Additionally, the rate of no resuscitation observed in this study is consistent with that of other ambulance services in Australia and New Zealand[33]. End of life care is an increasingly important part of appropriate OHCA management and through additional knowledge, greater experience and more patient-specific guidelines[52], is an area of care in which paramedics are becoming more informed and proficient.

Another finding providing further validation of more positive outcomes following OHCA events is the significant decrease over time in incidence of survival to <30 days after adjusting for age and gender (Publication 5) (although this was not observed in crude rates, or after adjusting for ARIA and gender, or SEIFA and gender). This reduction in incidence to survival <30 days is likely a direct reflection of the increase in survival to 365 days+.

The observed increased incidence in preferred pre-hospital and long-term outcomes is an extremely positive finding, but it must be remembered that survival is not a direct quality of life measure, which are more informative to the burden on person and public health. Nevertheless, survival (vs death) can be considered an indicator of quality of life, with longer survival measures being more indicative of a preferred quality. Quality of life measures, such as the ability to work/self-care, can be difficult to obtain. They are not included in routinely collected administrative or clinical data, and usually involve direct contact with patients and their family. This makes collection of quality of life measures time consuming and often unsuccessful. Due to the nature of cardiac arrest and the personal/emotional/psychological aspects involved, ethics committees usually require extensive procedures in place to ensure patient and family safeguarding. Collection of quality of life measures was beyond the realms of this study. This is noted as a limitation of this work and recommendations include their inclusion in future studies.

Increasing age is not only a risk factor for OHCA, but in the event of OHCA it is a widely reported predictor of worse outcomes[53-55]. This was evidenced in the findings presented in this thesis relating to the observed increase over time in incidence of survival to 365 days+, which was largely attributable to the age groups incorporating 45-64 years, accompanied by the lack of observed change in age-groups of 65 years+ (males and females). The much smaller number of events in age-groups of <35 years and the consequent reduced power make interpretation regarding results observed in these age groups limited. There was also some evidence that increasing age is a predictor of worse pre-hospital outcomes, in that the increase over time in Sustained-

ROSC was significant across both genders in the 45-64 year age-group, and although there was significance overall in the 75 years+ age-groups, it was not across both genders (only evident in males of 85 years+).

There are mixed reports in the literature regarding the impact of gender on outcomes. We know that females have a reduced risk of OHCA, so it seems a reasonable expectation that females may also have more better outcomes in the event of OHCA. This was not supported by the findings presented in this thesis. In this thesis, incidence of total OHCA events was higher in males than females, but there was also a higher incidence of all outcomes in males than females. Incidence of the most preferred pre-hospital outcome (resuscitation with sustained ROSC) was more than two times higher in males than females, and incidence of the most preferred long-term outcome (survival to 365 days or beyond) was more than three times higher in males than females. This suggests that in the event of OHCA, males are more likely to have preferred outcomes than females.

Interestingly, despite no significant changes over the 13-year study period in survival to 365 days+ in those aged more than 65 years, there was a significant increase in survival to 30-364 days in females (but not males) aged 75-84 years. This was an unexpected finding and requires further investigation.

Geographical remoteness

People living in more rural and remote areas have a worse general state of health and poorer healthcare outcomes than those living in major cities[41, 56]. This is for a variety of reasons, including less access to health care services, and in the context of the pre-hospital setting, the result of longer response times. It is important to ascertain the extent of this problem in relation to OHCA, so investigation into geographical remoteness was included in this programme of work. Previous studies, none in Queensland, have explored outcomes from OHCA by remoteness[57-62], but there are no published studies where incidence has been reported by outcome and remoteness.

Incidence rates and temporal trends over time of total events of OHCA by remoteness:

This programme of work shows that risk of OHCA generally increases with remoteness. Incidence of total OHCA events (and therefore risk of an event) was significantly higher in inner regional, outer regional and very remote areas, than major cities. These findings suggest there is a remoteness gap, in that there is less risk of OHCA in people living in major cities compared with more rural areas. Rates of OHCA increased over the 13 years of the study in both genders in major cities, inner regional and outer regional areas, and in males (not females) in remote areas. Collectively these findings indicate the gap is not worsening, and prevention strategies are likely penetrating all remoteness categories. In fact, the lack of significant increasing trend in females in remote areas and both genders in very remote areas may suggest a reduction in the remoteness gap over the time period of this study. However, these findings may also be due to the smaller number of cases in these areas, and therefore reduced power.

Conventional strategies to improve public health have historically been less successful in more remote locations which has presented a challenge to health care services. People in more rural locations have had less ability to access medical services and therefore reduced frequency to medical contact[56]. This has led to delays in (or lack of) diagnoses, treatment and access to specialists and specialist procedures; reduced hospital admissions; and reduced compliance[56]. The barrier of distance and the associated long travel times and prolonged periods away from home, also impact decision making on treatment pathways once conditions have been diagnosed. Additionally, largely due to necessity, people in more remote locations have historically had a more stoic attitude to health care than those less rural and been less inclined to seek out assistance[63].

Health care strategies targeting people in more rural and remote locations which have been implemented in recent years including mobile and pop-up healthcare clinics; enforced periods of service in rural and remote locations for healthcare workers; community engagement through education activities on when to access assistance; and telehealth programmes. Strategies such as these assist to improve the general state of health in rural and remote locations, which in turn, may reduce the risk of OHCA.

Incidence rates and temporal trends over time of OHCA by outcome and remoteness:

The findings presented in this thesis demonstrate that in the event of an OHCA, residents of more rural/remote locations are at greater risk of poorer outcomes, compared to those who live in major cities. This was evidenced by a higher overall incidence of the least preferred outcomes of events (no resuscitation and no ROSC) in inner regional, outer regional and very remote areas, compared with major cities; an inverse association between admitted cases and remoteness; and reduced overall incidence of sustained-ROSC and survival to 365 days+ in outer regional areas and beyond, compared to major cities.

As described for total OHCA events, analyses in temporal trends of specific outcomes from OHCA events suggests that the remoteness gap is not increasing and may be starting to close. Evidence of this includes significantly increasing rates over time in OHCA resulting in sustained ROSC (the most preferred pre-hospital outcome) in all remoteness groups except very remote (i.e., major cities, inner regional, outer regional, remote), and an increase in survival to 365 days+ within all remoteness categories. These are positive findings and again suggest that implemented strategies to improve outcomes from OHCA are penetrating all remoteness categories. As per prevention strategies, conventional strategies to improve outcomes from health conditions including OHCA, have previously been difficult to implement in more rural areas. For example, there has been reduced or no access to the same required resources in more rural areas as major cities, such as proficient bystander CPR educators. In more recent times rural-specific strategies have been implemented by QAS including community engagement initiatives[2, 5] such as the CPR Awareness and community bystander-CPR education campaigns, recruitment of community responders and greater engagement with rural Local Ambulance Committees (LACs). Public access defibrillator programmes have also been instigated, alongside community education from other government and non-government agencies, all targeting more rural and remote locations.

The lack of change over time observed in the most preferred pre-hospital outcome (sustained-ROSC) in those living in very remote areas should not be ignored and suggests there is still work to be done. It was not possible to independently assess this effect in relation to longer-term outcomes (survival to 365 days+), because remote/very remote were combined into one category due to small numbers.

Interesting findings requiring further investigation:

There was an absence of observed change in the incidence of OHCA events resulting in no resuscitation in the remote and very remote categories, but a significant increase in major cities, inner regional and outer regional areas (for both males and females, respectively). Due to longer response times, it is unsurprising that the rate of events resulting in no resuscitation in more remote areas is likely to be lower than in less remote areas, so changes resulting in a more selective application of resuscitation attempts, as previously discussed, have not impacted these areas to the same extent. Nevertheless, this variation by remoteness in OHCA events resulting in no resuscitation requires further investigation.

An interesting finding was the observed increase in incidence over the 13 years of the study in OHCA resulting in survival to 365 days+ in females of major cities and also in remote/very remote areas, alongside the lack of observed significant change in inner and outer regional areas. A possible explanation is type 2 error, however if type 2 error is present, the most likely scenario would be no observed change in incidence of these events in remote/very remote areas, as the number of cases in this category is by far the lowest (remote/very remote n=6; outer regional n=55; inner regional n=77; major cities n=194). This may in fact be due to some other bias (measurement or selection), as all the cases in that group occurred from 2011 onwards. It may also reflect a real finding in that remote specific strategies have been successful yet focused and resulted in a lack of improvement in the mid-remoteness categories. This requires further investigation.

Also interesting is that the lowest rates of total OHCA events and most outcomes (other than No-Resus and survival to <30 days) were observed in remote or remote/very remote areas. This finding is worthy of further exploration.

Reducing the remoteness gap in health status and outcomes has been a point of focus for the government and health services for some time. This programme of work demonstrates that there is a gap in relation to OHCA risk and resulting outcomes, but there is also evidence that positive progress has been made and that the gap has stabilised, if not reduced. Continued focus and new innovative strategies to penetrate rural and remote areas are a necessity in order to maintain this.

Socio-economic status

It is well documented that people living in lower socio-economic groups have a poorer state of general health, a greater risk of deteriorating health, greater rates of disability and live shorter lives, than those living in higher socioeconomic groups[41, 64, 65]. This is likely due to higher exposure to risk factors. The socio-economic gap is evident in cardiovascular disease[66], but the extent to which this gap is present specifically in risk to OHCA and outcomes from OHCA has not been ascertained. This is important to inform strategy development in this area, so socio-economic status was explored in this programme of work.

Incidence rates and temporal trends over time of total events of OHCA by socio-economic status:

This body of work highlights that incidence (and therefore risk) of an OHCA event generally decreased as SES increased. Importantly, risk of an OHCA event increased over the duration of the 13 year study period in the categories of lower relative advantage (SEIFA 1&2, 3&4 and 5&6), whereas there was no observed significant change in the groups of highest relative advantage (SEIFA 7&8 and 9&10). This is concerning and strongly suggests that prevention strategies need to be targeted towards lower socio-economic groups.

Incidence rates and temporal trends over time of OHCA by outcome and socio-economic status:

The results presented in this thesis also suggest that poorer pre-hospital outcomes are associated with relative disadvantage. Incidence was lower in people living in areas identified as highest advantage than in lowest advantage for every pre-hospital and long-term outcome, but the magnitude of difference was greatest for the least preferred outcome. That is, incidence of the least preferred outcome in this study (OHCA resulting in no resuscitation) was 30% lower in those living in areas of highest advantage relative to lowest advantage. Incidence of the most preferred outcome in this study (survival to 365 days or beyond) was 11% lower (and this was not a significant difference). This indicates that preferred outcomes are more frequent in those of higher SES.

Relative disadvantage is linked with factors known to increase risk of OHCA and/or poorer outcomes, such as smoking, obesity, hypertension, chronic disease and its management, lower rates of bystander CPR, and prolonged collapse to call time. The chronic disease epidemic is more prevalent in the lower socio-economic groups[66]. Therefore, the reduced risk of events resulting in no resuscitation amongst the lower socio-economic groups could reflect more patient-specific and evidence-based decision-making regarding resuscitation attempts. The specifics of this require further investigation and should be deemed a priority in order to address this increasing problem.

This programme of work also suggests that strategies implemented by QAS to improve outcomes from OHCA have penetrated all socio-economic groups. Incidence of OHCA resulting in sustained-ROSC significantly increased over time for all SEIFA categories (except females in the highest level of advantage, which was the only sub-group where there was no significant trend). Additionally, incidence of survival to 365 days+ increased significantly in all SES categories (although the increase in SEIFA 3&4 was not significant). These are positive findings.

The association between socioeconomic status and survival to 365 days+ was modified by gender, in that increasing trends were only apparent in males, with no trends observed for females in any of the SES categories. Part of this effect may be due to type 2 error, but this is an interesting finding requiring further investigation. When considered alongside the previously described more pronounced increase in total OHCA events in females than males suggestive of a greater impact of the chronic disease epidemic on females, this latter observation (survival to 365 days or beyond increased over time in males but not females) may be another indication that future strategies to reduce OHCA and improve outcome require a greater female focus.

Another interesting finding is that the only significant temporal trend in relation to total OHCA resulting in admission to hospital was an increase over time in the mid-range category (SEIFA 5&6) which was apparent in both genders. It may be that strategies targeting socio-economic groups of lower relative advantage have been implemented and penetrated only the mid-range categories, or there may be another explanation.

An anomaly worthy of further investigation appeared in people categorised as high (but not the highest) relative advantage (SEIFA 7&8), in that the highest incidence rates of total OHCA events and of every pre-hospital and long-term outcome were observed in this group. Similar results have been reported in other population-based health care studies in Queensland, which are equally puzzling (e.g.,- rates of all cancer, and also of major cancers such as breast, prostate, colorectal, tracheal/bronchus/lung, and melanoma, were highest in SEIFA categories 7&8[67]).

Aim 3: To investigate predictors of survival from OHCA

Aim 3 of this thesis was addressed in Chapter 7 (Publication 6). Previous studies have investigated predictive factors of OHCA using multinomial logistic regression[53-55], but this is the first published study to use this method of analyses utilising pre-hospital identified cases and long-term outcomes, including survival to 365 days+, and the first study using multivariate analyses to identify independent predictors of outcomes from OHCA in Australasia.

Factors independently positively associated with survival to 365 days+ include cases with an initial shockable rhythm, bystander witnessed events with bystander CPR, paramedic witnessed events, and age which was inversely associated with survival to 365 days+ (for every year of age, survival to 365 days+ reduced by 4%). These are all commonly reported independent predictors of outcomes[3, 35-37, 53-55] and factors that previous and current pre-hospital strategies are designed to address. Although expected, these findings usefully inform future guideline strategy development and practice.

The most meaningful and novel finding of this study was the observed 53% increase in survival to 365 days+ in cases with CCP attendance. There is extensive evidence to suggest that the advanced skills of CCPs do not result in preferred outcomes[17, 68-72]. One explanation for this finding could be the advanced knowledge, increased experience and greater ongoing exposure to high acuity cases of CCPs in comparison to ACPs, which lead to a better application of non-technical skills such as communication and leadership. When applied effectively, non-technical skills create a more composed, structured, organised and efficient scene which results in higher quality patient care and more patients with preferred outcomes. The importance of non-technical skills in emergency care is increasingly being recognised[13, 14, 73] and this explanation for the observed findings is concurrent with other out-of-hospital studies showing results in favour of a team-focused, coordinated approach[15, 26, 74, 75]. Another possible explanation is that the effect is due to the presence of an additional paramedic on scene. It was not possible to adjust for the number of paramedics on scene. This is important because presence of an additional paramedic of any level at a resuscitation may impact outcome either positively or negatively. While possible, it is unlikely that this is the reason for the observed finding, as there are often additional resources on scene (such as OICs, students or observers). Additionally, the little research done in this area suggests no differences in effectiveness of CPR and time to performance of BLS or ALS procedures between a crew size of 2, 3 or 4[76].

This observed association between CCP attendance and improved long-term survival in collaboration with the recommendation of immediate implementation of a modified resuscitation protocol preferably alongside pit crew approach (within Aim 1 of this thesis), provides evidence that a specifically structured pathway using a designated CCP as a scene team leader largely with no clinical role, could be extremely successful. The preferred application of this would require a specifically designated resource and the provision of frequent standardised training to consolidate and practice the skills required. It is likely the use of checklists, experts in this field, real case video/auditory recordings and effective educational audit processes would contribute to the most efficient practice. A well-practiced strict pit crew model is difficult to achieve in the pre-hospital environment due to the lack of a consistent team to each case, but this strategy provides the best feasible solution. This is supported by a study showing improved resuscitation performance when one member of the team was trained in effective leadership[77]. This strategy would also provide a platform and oversight for future clinical trials and/or the addition of new practices or equipment such as a mechanical chest compression device (as recommended in Aim 1 of this thesis).

Successful intubation was positively associated with survival to <30 days and 365 days+, but the association was stronger for survival to <30 days. LMA placement was not associated with any outcome. Resuscitation attempts of lesser duration due to recognition of futility shortly after commencement leading to no ROSC, do not usually involve placement of an advanced airway. In longer resuscitation attempts, LMA use is the first line advanced airway and usually sufficient, so intubation is usually only required in prolonged resuscitation or patients with complex airways. Unfortunately, it was not possible to adjust for length of resuscitation in this study, so this cannot be ruled in or out as an explanation for the observed findings.

The lack of ability to adjust for length of resuscitation attempt in this study is also a possible explanation for the observed inverse association between adrenaline and all outcomes, when compared with events resulting in no ROSC. Adrenaline administration is one of the later interventions to be undertaken in a resuscitation. Alternatively, these results may reflect a true negative effect from adrenaline as suggested in a previous study which did adjust for no and low flow times[54]. The use of adrenaline in cardiac arrest has been a long-standing point of controversy. A recent large rigorously designed RCT (PARAMEDIC 2)[78] investigated this and found 30-day survival, survival to discharge and 3-month survival significantly higher with adrenaline use than placebo, however, there were no between group differences in survival to hospital discharge and/or to 3-months with favourable neurological recovery (defined as Modified Rankin Score of 3 or less).

In this study, between midday-2.59pm was positively associated with survival to 365 days+, while 9pm-11.59pm was inversely associated. Possible explanations are increased likelihood of an event being witnessed, increased availability of paramedics/ED staff with shift cross over periods around midday-2.59pm, as well as better access to other specialist resources, and the opposite around 9pm-11.59pm. Any or all of these factors potentially increase/decrease response and definitive care intervals.

Geographical remoteness was inversely associated with survival to 365 days+. Odds of long-term survival were lower in people living in inner regional, outer regional and remote/very remote areas, when compared with major cities, although the only significant association was for outer regional areas. This is consistent with reports of a remoteness induced health care gap[57, 79] and with findings from Aim 2 of this thesis which found increasing incidence of survival to 365 days+ over time in all remoteness categories, apart from in females living in inner regional areas (rates increased but not significantly, and outer regional areas (rates remained stationary). It may be that remote specific strategies implemented and promoted by the QAS in recent years[2, 5] have been successful, yet focused, leading to a lack of effect in the mid-remoteness groups. This phenomenon requires further investigation which was outside the scope of this study.

In this study, there was no observed association between socio-economic status and survival to 365 days+. Previous research has shown an inverse association with positive outcomes[80, 81], so this could represent a positive finding demonstrating progression in reducing the socio-economic health gap. This complements the findings relating to Aim 2 of this thesis, which showed evidence that implemented strategies have penetrated all socio-economic groups (incidence of sustained-ROSC increased significantly over time for all categories and incidence of survival to 365 days+ increased significantly in all categories apart from SEIFA 3&4).

General findings

Outcomes from OHCA have been routinely collected for some time using standardised measures. Those commonly reported include sustained-ROSC, survival to admission, survival to 24 hours and survival to 30 days[82]. This body of work used mutually exclusive outcomes that reflect commonly reported outcomes, and importantly, longer term survival was investigated in this study. Survival to 30-364 days was used in this work, which distinguishes between survival to 30 days or more and survival to 365 days or more. This group (survival 30-364 days) contained very few patients in comparison with the other groups, which highlights uncertainty about the most useful end point for long-term outcome. Further exploration using survival analysis may better inform a more useful survival time period than the periods currently most frequently used. It must be remembered that survival is not a quality of life measure, however there may be one or more lengths of survival that are most indicative of quality of life.

Strengths and limitations

The strengths and limitations of each Chapter have been discussed in the relevant Chapter. Below is an overview of the strengths and limitations of the overall programme of research.

Strengths

Data Linkage

Use of rigorous data linkage methodology (using deterministic and probabilistic linkage). Data linkage strengthened the study in three main ways:

i. *By providing additional variables on an individual patient level and long-term outcomes (365 days+)*. All patient information beyond the point of hospital handover would have been unavailable if The QAS OHCA Registry had been used in isolation. Data linkage enabled access to these variables including those required to calculate the long-term outcomes (e.g., survival to beyond 365 days) specifically required for this study. This is a novel and important point of difference between this study and previous work published in this area. This is the first Australasian study known to the author and advisors where incidence of pre-hospital attended OHCA has been examined by long-term outcome, over such a significant time period.

ii. *By providing multiple sources of information for the same variable (e.g., age, gender and postcode).* The collection of these variables from multiple sources facilitated the collation of a more accurate and complete final dataset for analysis. Due to the lack of bystander knowledge and the short window paramedics have to collect information, residential postcode is often missing in pre-hospital data. Data linkage allowed the capture of residential postcode recorded within hospital and death records and therefore facilitated the identification of Queensland versus non-Queensland residents (required to calculate accurate incidence rates). If the QAS OHCA Registry alone were used, residential postcode would have only been available in 21,335 cases (66%), whereas after data linkage, residential postcode was available for an additional 9,885, increasing capture to 31,220 cases (97%). Additionally, this facilitated investigation of geographical remoteness and SES which were both derived from postcode, and which are previously under-explored variables. This represents a second novel and crucial difference between this programme of work and previously published studies. There are no other Australasian studies known to the candidate (and advisors) where incidence of OHCA have been investigated in relation to remoteness and socioeconomic status, over time, for pre-hospital and long-term outcomes.

iii. *The avoidance of high loss to follow-up rates.* This study has 99.2% data linkage sensitivity, meaning there is minimal selection bias.

Date linkage therefore overcomes some usual limitations of pre-hospital research and has also contributed substantially to the evidence on OHCA.

Population-based Approach

In this study, data were extracted from three routinely collected administrative databases that encompass the whole state of Queensland. This population-based approach minimises the likely presence of measurement and selection bias. Additionally, the case identifying dataset (QAS OHCA Registry) collects all cases of OHCA attended by QAS paramedics in Queensland, using rigorous collection and reconciliation methods, so achieves near 100% capture.

The population-based approach to calculate incidence, as opposed to previously reported proportions, was essential to accurately identify groups at-risk of OHCA and predictors of outcome, both of which are important to inform preventive strategies to improve public health.

Mutually Exclusive Outcome groups

Analyses for this study used mutually exclusive outcome groups. This method is atypical when reporting OHCA outcomes, however, allowed the exploration of characteristics of each group independently, which fills a gap in the evidence base. This also allowed epidemiological analyses such as relative risk, which cannot be done otherwise and was an aim of this thesis.

Temporal Trends

A broad study inclusion period (2002-2014), representing 13 calendar years, was used for this study. This gave scope for meaningful analyses of temporal trends and ensured a large sample, allowing stratification for various factors with reduced risk of type 2 error.

Collectively, these factors allowed the calculation of reliable and accurate population-based incidence rates of OHCA by outcome over a period of time by age and gender, and stratified by important, previously under-investigated factors such as remoteness and socioeconomic status. These results are representative and generalisable, and the programme of work has facilitated some novel and compelling findings.

Limitations

This was an observational study and therefore the findings must be interpreted in the context of inherent biases.

Causality

Firstly, causality cannot be assessed using an observational study design, however this was not the focus of this study

Using Postcode to Estimate Socioeconomic status / Geographical Remoteness

SEIFA is a broad measure of SES which is applied by region, rather than individually to a person, hence this aggregated area-level measure of socioeconomic disadvantage may not accurately represent all individuals living in the area. Similarly, using residential postcode to estimate geographical remoteness is not without challenges. There is more than one ARIA code assigned to some postcodes, which may have resulted in misclassification of some cases. However, within the context of the very large number of cases in this study, the small number of cases whom this may have affected is likely to be negligible.

Administrative Data

There are limitations associated with using large administrative datasets. The utility of the data relies on the dataset accuracy, completeness and consistency at source. However, each of the three datasets accessed for this study operate under rigorous collection and reconciliation processes that are closely monitored. Accessing data across a substantial period of time also results in challenges, due to inevitable changes in data administrators, addition/subtraction of variables, and updated definitions. When there are three different data sets being combined, these challenges are compounded. There are likely limitations of the datasets used, such as coding intricacies (varying coders and coding practices over time) and level of completeness (although for the variables investigated this is likely to be very low).

Confounders

While this programme of work did include confounders that have not previously been studied in this level of detail (remoteness, socioeconomic status), there were some potential confounding factors not addressed. For example, sample size prevented calculation of temporal trends of OHCA by outcome simultaneously adjusting for age, gender, socioeconomic status and remoteness. When examining the predictors of survival from OHCA (paper 6, Chapter 7), it was not possible to adjust for number of paramedics on scene, length of resuscitation attempt, or experience of previous OHCA event/s. Finally, there are confounders that could not be analysed in this study because they do not appear as variables in the routinely collected data that was linked for this study (e.g., variables such as smoking, alcohol consumption, underlying health conditions/comorbidities, access to and participation in rehabilitation, etc). Some of these factors such as collapse to call interval, length of resuscitation and CPR quality (bystander and QAS), are known to have an impact on outcomes from OHCA, so not being able to adjust for these variables is a limitation that must be considered when interpreting the findings.

Sample Size

While this was a population-based study, there are small numbers in some sub-groups, resulting in the likely presence of type 2 error in some calculations, which restricts meaningful interpretation for these groups. For instance, in publications 3 & 4 (Chapters 4 & 5) there were very few younger aged adults (18-24years and 25-34 years) who experienced OHCA resulting in Unsustained-ROSC (n=0 and n=5 respectively), and few people living in very remote areas who had an OHCA (n=361). Consequently, some 95% confidence intervals were broad and included 1.0 for some associations.

Extended Data Period

Various changes occurred during the 13 years of data collection. There were changes in ILCOR guidelines (including less focus on ALS procedures and more emphasis on CPR quality and early defibrillation)[50], and new monitors/ defibrillators were introduced. Concurrently, paramedic education developed and there has been an increasing general focus on OHCA management in QAS[1, 2]. These factors all likely have a positive impact on survival.

Indigeneity / ethnicity

This study does not include investigation into risk and outcome from OHCA by indigenous status or ethnicity. There is a known indigenous health gap Australia wide and Queensland has an indigenous population that is higher than the national average[83], so an investigation into the association between Indigeneity and OHCA is an important piece of work. This was beyond the scope of this thesis.

Quality of Life

Quality of life measures were not captured in any of the datasets utilised for this study. While this was not the intent of the programme of work, it must be acknowledged that even in those who experience the most preferred outcome from OHCA (survival beyond 365 days), there are varying degrees of quality of life that may occur. Investigation of the impact on quality of life using validated quality of life measures would require prospectively and individually following up patients who experience OHCA for a period of time, which was beyond the scope of this programme of work.

Generalisability

Finally, while this was a population-based study and included every recorded case of OHCA attended by QAS paramedics in Queensland during the study period, it is acknowledged that the study relates only to Queensland. While it is likely that these results can be generalised to other states in Australia and similar other countries where the population dynamics and characteristics are similar, it is possible that the findings may not be generalisable beyond these populations, or in settings where the definitions or system practices vary markedly from that used in Queensland.

Implications for policy, practice and research

This programme of work yields several important implications for policy, practice and research. These have already been discussed throughout the thesis in the context of each of the manuscripts, but also in the preceding thesis Discussion where relevant. These are summarised as Recommendations for action below.

Policy and Practice

- Within the pre-hospital setting, there should be continued focus on patient-specific decision making
- Rural-specific strategies to reduce OHCA and to improve outcomes (such as community engagement initiatives) should be continued and preferably further developed e.g., an extended use of volunteer first responders
- OHCA prevention and management strategies targeting lower socio-economic groups require focus
- Long-term outcomes (such as survival to 365 days or beyond) should be incorporated into routine reporting
- Implement a strategy whereby a specific resource with specialist scene control and leadership skills for OHCA is dispatched to all OHCA cases (supported by literature review and findings of paper 6)
- Implementation of mechanical chest compression device for cases in which it has practical advantages. Processes need to be in place to ensure this is done safely
- Focus on the development of appropriate end of life care

Research

- More robust rigorous studies into pre-hospital resuscitation strategies generally, especially those identified in the review where there has been little research to date (i.e., Passive oxygen insufflation, hypertonic saline administration, erythropoietin administration, lignocaine administration prophylactically, procainamide administration, waveform analysis guided shock timing)
- Focused investigation into the observation in this thesis of fewer cases (per 100,000) of OHCA in remote areas (relative to major cities, inner and outer regional areas, and very remote areas)
- Exploration of the apparent higher rates of OHCA in areas of moderately high socio-economic status (SEIFA categories 7&8)
- Further investigation into potential reasons for the observed increase in survival beyond 365 days with CCP attendance, while adjusting for length of resuscitation and number of paramedics on scene. This requires very large population-based studies, possibly across several pre-hospital services (if conducted in Australia)
- Investigation into a meaningful measure of survival (for example using survival analysis), as opposed to the routinely used “survival to 30 days”. In this thesis, there were very few cases (n=113) in the “survival 30-364 days” category, versus much larger numbers in other categories (ROSC to/at hospital, and survival to 365 days+). This suggests that those who survive to 30 days are likely to survive beyond 365 days+. Survival analysis may help to identify a more appropriate cut-point
- Investigation into the pronounced increase over time in total OHCA events observed in this study in middle aged females (45-64 year age groups)
- Further study is required involving validated Quality of Life measures for patients surviving OHCA. This needs to be well-resourced as it will require making contact with individuals who experience an OHCA in a large, prospective study with a reasonable follow-up period

8.3 Thesis Conclusion

OHCA is a major global health issue worldwide which has low survival and is a large burden on public health. This study provides broad analyses of recent literature regarding strategies to improve outcomes after OHCA, and in-depth epidemiological analyses of a large, population-based linked dataset of 13 years of pre-hospitally attended OHCA by pre-hospital and longer-term outcomes. These epidemiological analyses facilitated novel and compelling evidence regarding remoteness and socioeconomic status, which have to date been underexplored, and for which there is a known health care gap. Collectively, these provide essential information for QAS and other developed ambulance services to evaluate implemented strategies and inform future policy and strategy development, alongside service provision. This work provides an important addition to the pre-hospital evidence base and contributes towards excellence in patient care at a population level.

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Appendix A: Other related publications during candidacy

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Appendix B: Evidence of the fulfilment of copyright requirements

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Appendix C: Presentations during candidacy

Kenneth James McPherson conference, 2013. Oral presentation - Surviving Out of Hospital Cardiac Arrest – Past, Present and Future

PhD Confirmation Seminar, March 2014. Oral presentation - Resuscitation Strategies in Out-of-Hospital Cardiac Arrest (OHCA) to Improve Outcomes

Presentation to Paramedic Science staff and students at Queensland University Technology (QUT), 2015. Oral presentation - Translating evidence into clinical practice

Cairns Paramedic Symposium, 2015. Oral presentation - Research in out-of-hospital cardiac arrest patients

Paramedics Australasia Conference Gold Coast, 2014. Poster presentation - Epidemiological analysis of Adult Patients who Experience Out-of-Hospital Cardiac Arrest

Australian Resuscitation Council Spark of Life Conference Adelaide, 2017. Poster presentation – Temporal trends of incidence and shockable status of adult out-of-hospital cardiac arrest (OHCA) of presumed cardiac aetiology in Queensland

Paramedics Australasia Conference Ipswich, 2017. Oral presentation – Out-of-hospital research: Everyone has a role

PhD Pre-completion Seminar, Townsville 2019. Oral presentation - Out-of-hospital cardiac arrest (OHCA) in Queensland, Australia - Epidemiology and predictors of outcome

Appendix D: Glossary

Definitions used for this study are concurrent with those of the Queensland Ambulance Service (QAS) Out-of-hospital cardiac arrest (OHCA) Registry [1] and the Queensland Hospital Admitted Patient Data Collection (QHAPDC) [2].

Cardiac arrest - The condition when a patient is unresponsive and pulseless

Out-of-hospital cardiac arrest (OHCA) – Any case where the patient has been in cardiac arrest while in the presence of QAS responders and the cardiac arrest has primarily been managed by those QAS responders (independent of location)

Resuscitation attempt – Where the total duration of the QAS resuscitation attempt ≥5mins or an ALS procedure has been attempted at any time during the cardiac arrest. If the resuscitation attempt is less than 5 mins and an ALS procedure was not attempted, the case is still classified as a resuscitation attempt if resuscitation was ceased because ROSC was achieved OR the patient was handed over to hospital care while resuscitation was still underway

Return of spontaneous circulation (ROSC) - The point at which spontaneous circulation is re-established, as identified by the presence of a sustained palpable pulse

Intra-arrest - During cardiac arrest

Post-arrest – Any time after ROSC

Cardiac aetiology – This is presumed in male persons ≥40 years old or in female persons ≥50 years old, when there is no evidence to suggest that another classification is more appropriate. This may be confirmed by the presence of cardiac related symptoms such as chest pain or evidence of a cardiac history. Cardiac aetiology may apply outside of these age ranges in the presence of cardiac symptoms, definitive recent cardiac history and / or ECG changes consistent with a cardiac aetiology [1]

Code 1 – The highest priority of ambulance response including immediate activation of the nearest available resource with use of emergency lights and sirens

Code 2 – An ambulance activation of the nearest available resource and immediate response without the use of emergency lights and sirens

Cardio-pulmonary resuscitation (CPR) – The provision of a combination of chest compressions and ventilations

Basic Life Support (BLS) - Resuscitation by means of CPR and use of a defibrillator. Basic airway adjuncts such as oro/naso-pharangeal airways may also be used in BLS

Advanced Life Support (ALS) - Resuscitation with clinical intervention beyond that of BLS. Eg. intra-venous (IV)/ intra-osseous (IO) access; IV/IO drug administration; advanced airway adjuncts such as laryngeal mask airway or endo-tracheal tube

Duration of a cardiac arrest - The point of first identification of cardiac arrest up until ROSC

Chest compression fraction (CCF) - The proportion of time (%) chest compressions are performed during a cardiac arrest

Electronic ambulance report form (eARF) – Completed by QAS paramedics for each attended case

Cardiac arrest report (CAR) Number – A unique number assigned to each case of OHCA identified by the ISREU

Death and cardiac arrest report form (DCARF) – A form completed by paramedics for each case of OHCA attended

Staff - This includes any person or persons representing the ambulance service ie. Critical Care Paramedics, Advanced Care Paramedics, Student Paramedics, Patient Transport Officers, Clinical Support Officers, Operations Supervisors, Medical Officers, observers

Local Ambulance Service Network (LASN) - A geographical area of Queensland. QAS consists of 16 of varying sizes which match Queensland Health divisions

International Liaison Committee of Resuscitation (ILCOR) - Committee made up of American Heart Association (AHA), European Resuscitation Council (ERC), The Heart and Stroke Foundation of Canada (HSFC), The Australian and New Zealand Committee on Resuscitation (ANZ-COR), Resuscitation Council of Southern Africa (RCSA), The Inter American Heart Foundation (IAHF) and The Resuscitation Council of Asia (RCA) who facilitate comprehensive reviews of resuscitation science to produce guidelines

References

1. Queensland Ambulance Service Cardiac Outcomes Registry - Coding Manual.
2. Queensland Hospital Admitted Patient Data Collection (QHAPDC) Manual 2015-2016 Version 1.0. 2015.

Appendix E: Legislation and governance

ILCOR use a robust system to identify and review international science and knowledge relevant to CPR for the purposes of regularly producing a document entitled 'International Consensus on CPR and Emergency Cardiovascular Care Science with Treatment Recommendations' (CoSTR) [1, 2]. This is a comprehensive document which includes recommendations on BLS, ALS, defibrillation, ACS, PLS and NLS. Evidently this requires international contributions. The current membership and contributors comprise: American Heart Association (AHA); European Resuscitation Council (ERC); Heart and Stroke Foundation of Canada (HSFC); Australian and New Zealand Committee on Resuscitation (ANZCOR); Resuscitation Councils of Southern Africa (RCSA); Inter-American Heart Foundation (IAHF); Resuscitation Council of Asia (current members Japan, Korea, Singapore, Taiwan) [1].

2005 Guidelines

Changes implemented in the 2005 ILCOR recommendations [3-6] which directly impact on the treatment algorithm used by paramedics to manage adult OHCA patients of cardiac aetiology:

1. Increased emphasis on the process of CPR: push hard at a rate of approximately 100 compressions/min^{-1}, compress at a depth of approximately 4-5cm, allow full chest recoil and minimise interruptions
2. Use of a compression-ventilation ratio of 30:2 replacing15:2
3. Change in ventilation length to one second rather than 1-2 seconds. When an advanced airway is in situ, ventilations are continuous at 8-10/min^{-1} with continuous compressions
4. Single shock rather than a triplet of shocks when a biphasic defibrillator used
5. Two minutes of CPR before defibrillation in an unwitnessed arrest
6. The immediate resumption of CPR post shock instead of prior cardiac rhythm analysis
7. Amiodarone administration for refractory VF/VT
8. Removal of atropine for asystolic arrests

2010 Guidelines

Changes implemented in the 2010 ILCOR recommendations [7-10] which directly impact on the treatment algorithm used by paramedics to manage adult OHCA patients of cardiac aetiology:

1. Airway, breathing, circulation (ABC) primary approach changes to CAB (circulation, airway, breathing)
2. Minimum of 100 compressions/min^{-1} rather than approximate
3. Minimum 5cm depth rather than 4-5cm
4. Chest compressions to continue during charging
5. In an unwitnessed arrest apply defibrillator and shock as soon as practical – no delay

The evidence which informed these changes falls within the following groups: Chest compressions; ventilations; defibrillation; and pharmacology.

Chest compressions

Prior to implementation of the 2005 ILCOR recommendations there was substantial evidence [11-16] indicating that interruptions and poor technique (including insufficient rate, depth and poor chest recoil) of CPR occur frequently both in and out of hospital. This, along with the increased recognition of the importance of high-quality CPR, highlighted the requirement for attention to CPR quality and was reflected in the 2005 recommendations (specifically points 1-6). This issue was later reinforced by evidence demonstrating a statistically significant association between quality chest compressions and ROSC [17, 18] and subsequent evidence [19, 20] demonstrating that the overall quality of chest compressions is poor. Hence the provision of good quality CPR was re-emphasised in the 2010 recommendations (specifically points 1-4).

Up to date evidence was used to ascertain a definition of high-quality CPR and inform the recommendations, as follows:

- **Minimal interruptions**

Minimal interruptions in the delivery of chest compressions was found to be a key element in providing the most efficient false circulation. It was well demonstrated that when compressions are stopped, coronary perfusion pressure reduces substantially and several compressions are required before it recovers to its previous level [21]. This concept was supported by multiple studies; animal [22-26] and human [15]; which showed that continuous chest compressions with minimal or no interruptions are associated with better haemodynamics, ROSC and survival. It was also demonstrated that interruptions in CPR is associated with a decreased probability of conversion of VF to another rhythm [15]. This resulted in a continued focus on the provision of continuous chest compressions with minimal interruptions.

In 2005, the recommendation of immediate resumption of CPR post shock (point 6) was a specific element to minimising interruptions. This interruption was required in order to defibrillate a patient but could become rather prolonged due to the post shock pulse check. An animal study [23] showed that longer delays for defibrillation worsened outcomes and it was found that palpable pulses were rarely present after defibrillation [16, 27] and so an immediate pulse check was largely unreliable anyway. Therefore, the recommendation was made. Subsequently evidence in the form of two human studies [28, 29] and 3 animal studies [26, 30] showed immediate resumption of chest compressions after defibrillation was associated with better survival and/or survival with favourable neurological outcome compared with immediate rhythm analysis and delayed resumption of compressions. This recommendation therefore remained unchanged in 2010.

In 2010, the recommendation of the primary approach changing to CAB as opposed to ABC (point 1) was introduced. This reduces the time to recognition of cardiac arrest and results in the commencement of resuscitation with chest compressions rather than ventilations. This also minimises the time to chest compression initiation, as evidenced by one manikin study [31]. This does also prolong the time to first ventilation however ventilations are increasingly being deemed as less important in the initial stages of resuscitation [24]. The use of ABC formed the basis of all primary surveys so this change was major for ILCOR. It is likely that it was not adopted in the 2005 recommendations;

as it was by the ERC; due to this and also due to the lack of evidence surrounding it, although in theory it is convincing.

- **Rate and fraction**

The number of chest compressions a patient receives per minute is dependent upon the rate and CCF. The recommended rate of chest compressions before 2005 was 100 compressions/min^{-1} [32-34] and since this there has been mixed evidence with regard to the optimum rate. Some studies showed improved outcomes with increased rates (>100/min^{-1}) and others showed no difference. However, it was strongly suggested that chest compression rates >80 were associated with ROSC [12]. Therefore in 2005 the recommended rate remained at approximately 100/min^{-1}, although there was an increased emphasis on achieving this. Subsequent evidence provided by the largest clinical investigation of its kind at this time demonstrated an increased chest compression fraction to be independently predictive of improved survival to hospital discharge [35]. Survival was highest when a fraction of >0.6 was achieved and the corresponding rate in this category was median 111 (Q1, 100:Q3, 123) [35]. The recommendation in 2010 therefore changed to a minimum of 100/min^{-1} with maintenance of emphasis on the importance of achieving this.

- **Depth**

Prior to the 2005 ILCOR recommendations, there was little new evidence to inform the specific 4-5cm recommendation for chest compression depth. Historically low level studies have shown that compression depths of 3-4 inches are associated with improved ROSC and preferred neurological outcome when compared with shallower compressions [36-38]. Due to evidence that chest compression delivery was frequently shallow [13], the 4-5cm recommendation was put in place as a reasonable estimate to provide quantification. This also emphasised the requirement for adequate depth. Subsequent studies on swine have re-emphasised the importance of adequate depth as follows: A depth of 5cm demonstrated greater restoration of ROSC, neurologically normal 24 hour survival and histopathologic findings when compared with 3.7cm [39]; A depth of 6cm was associated with preferred outcomes when compared with shallower depths [17]; and 25% anterior posterior displacement was associated with greater ROSC rates when compared with 17.5% displacement [40]. Human studies [41, 42] suggest that compression depths of 5cm or more may improve success of defibrillation and ROSC. There was no evidence to inform an upper limit so based on this evidence the recommended depth of chest compression was increased to a minimum of 5cm.

- **Recoil**

Complete chest wall recoil enhances negative intra-thoracic pressure. This acts as a vacuum promoting venous return, ventricular filling and flow. Allowing complete chest recoil also provides a period of time to allow adequate ventricular filling. Animal studies have shown significant reductions in mean arterial pressure, coronary perfusion pressure, cardiac output and myocardial blood flow with only small amounts of incomplete chest recoil during CPR [43, 44]. It was therefore recognised as an important element to high quality CPR. Low compliance with ensuring complete chest recoil was demonstrated in a study of EMS personnel [45], showing that in 46% of cases there was some residual and continuous pressure on the chest wall during decompression. As a consequence, the 2005 recommendations stipulated ensuring full chest recoil as a part of the provision of high-quality CPR.

- **Ratio**

The ratio of chest compressions to ventilations forms a balance between providing optimal flow and ensuring adequate oxygen availability for the tissues. The optimal ratio is likely to vary slightly for each patient dependent upon factors such as age, gender, aetiology, co-morbidities and many others, but the specifics of this would be largely difficult to ascertain and potentially confusing for rescuers. It is therefore important to have a standard ratio used for all adults in cardiac arrest.

Prior to 2005, the ratio of chest compressions to ventilations in adult CPR was 15:2. It was demonstrated that by using this ratio, maximal coronary perfusion pressure is only achieved for 33% of each compression–relaxation–ventilation cycle [21]. Some animal evidence [46] suggested that more compressions per cycle would be preferable and various other studies were undertaken yielding mixed specific results. However, 30:2 was suggested by mathematical analyses as the optimum ratio for use by health care professionals to provide best flow and oxygen delivery [47]. Consequently, this ratio was introduced in the ILCOR 2005 recommendations.

Other larger ratios were investigated, such as 100:2 which was associated with a lower ROSC rate and reduced arterial partial pressure of oxygen [48] when compared to 30:2. The benefits of 30:2 versus 15:2 was further reinforced [49] and ratios of 50:2 or 100:5 demonstrated no benefit over 30:2. This ratio therefore remained unchanged for the 2010 recommendations.

Ventilations

Prior to 2005, ILCOR recommendations specified that the length of each artificial ventilation during CPR should be 1-2 seconds [34]. There was no recommendation for ventilations to be continuous when an advanced airway was in situ, so compressions were still routinely interrupted for ventilation pauses. There was evidence suggesting that experienced paramedics performed ventilation at excessive rates (specifically on intubated patients) during treatment of OHCA [50]. It was also suggested that hyperventilation was associated with increased intrathoracic pressure, impedance of venous return, decreased coronary and cerebral perfusion and decreased ROSC [50, 51]. These studies also demonstrated that when an advanced airway is in place, ventilation rates of>10/min and inspiration times>1 sec are associated with no survival. Subsequent evidence showed that ventilation rates of 6 per minute are associated with adequate oxygenation and better haemodynamics than ≥12 per minute [52]. These studies all highlighted the requirement for attention to ventilation recommendations and adherence to them. The change made to recommendations in 2005 (point 3) not only stipulates a more appropriate ventilation length, but as a result contributes towards minimising interruptions in chest compressions and eradicating interruptions for purposes of ventilation when an advanced airway is in situ, which both further optimise chest compression fraction.

Subsequent evidence demonstrated there was no clinically important difference in tidal volumes when a 1sec or 2sec inspiratory time was used [53-55]. Consequently, this recommendation remained unchanged in 2010, only with increased emphasis on the importance of minimising ventilations.

Defibrillation

ILCOR introduced the single shock strategy into recommendations in 2005 (as per point 4). Prior to this, shocks would be administered in groups of 3 and only interrupted if ROSC was achieved or the rhythm became non-shockable. Defibrillator technology is continually evolving and by 2005 new defibrillators largely shocked with a biphasic waveform as opposed to the previous monophasic. Various studies demonstrated that defibrillators which administer a biphasic waveform have a higher first shock success rate than monophasic [56-58]. This was shown to be as high as 96% and significantly higher than monophasic controls [58]. This evidence combined with the increasing awareness of adverse factors associated with interruptions in chest compressions gave status to the one shock strategy.

Since this implementation there has largely been no further evidence to support the one shock strategy. Three pre-post designed studies showed significant survival benefit with a single shock protocol compared with three stacked shocks [28, 29, 59]. However, these had multiple potential confounders and multiple interventions so the true attributable value of the single shock strategy specifically is largely unknown. A further study showed no benefit from a protocol that included a single shock protocol compared to 3 shock protocol [60]. However, a study with fewer confounders shows a significantly lower hands off ratio with the one shock protocol but no survival benefit [20]. Although the benefits of this strategy appear to be largely non-evidenced in more recent literature, the theory and previous studies are convincing and there are known benefits associated with lower hands-off ratio. Consequently, this remained unchanged in the 2010 recommendations.

Also implemented in 2005 was the introduction of two minutes of good quality CPR before attempted defibrillation in an unwitnessed arrest (as per point 5). This is due to theory that hypoxic myocardium (as is most likely in an unwitnessed arrest) is less likely to be in course VF and therefore less likely to be successfully defibrillated. The initial two minutes of CPR is intended to re-oxygenate the myocardium and increase the likelihood of course VF and therefore successful defibrillation.

One pre-post designed study showed that 90 seconds of CPR prior to defibrillation was associated with increased survival when response times were 4 minutes or longer [61] and one RCT showed that patients in VF who had an ambulance response interval >5mins and received 3 minutes of CPR prior to defibrillation, had better outcomes than standard treatment of immediate defibrillation [62]. This evidence resulted in the 2005 change of recommendation. After this recommendation, multiple studies were published to suggest there was no benefit.

In two RCTs a period of 90 seconds [63] or three minutes [64] of CPR by EMS personnel before defibrillation did not improve ROSC or survival to hospital discharge in patients with out-of-hospital VF/pulseless VT, regardless of response interval. One large (n=1638) prospective multi-centre study [65] of first rhythm VF/VT patients showed the odds of survival to be greater with 46-195 seconds on CPR before defibrillation compared to <45 seconds of CPR before defibrillation but an optimal CPR duration was not achieved and no duration achieved statistical significance. A further study [66] showed no significant improvements in ROSC or survival to hospital discharge when a strategy of CPR before defibrillation was compared to a shock first strategy. However, the CPR first group showed a higher rate of favourable neurological outcome at 30 days and 1-year post arrest. Largely the evidence for the CPR first strategy is inconsistent and therefore in 2010, the recommendations reverted back to application of a defibrillator and shock as soon as possible.

Pharmacology

Amiodarone was introduced in the ILCOR 2005 guidelines (as per point 7) for patients in refractory VF/VT. This was as a result of two RCTs specific to this subset of patients treated by paramedics in the out-of-hospital setting. The first was undertaken in Seattle and suburban King County, US and was a amiodarone versus placebo trial [67]. Patients who received amiodarone were significantly more likely to survive to hospital admission than those in the placebo group (44% versus 34%, (p=0.03)). The adjusted OR for survival to hospital admission in the amiodarone group compared with the placebo group was 1.6 (95%CI: 1.1-2.4 (p=0.02)). The trial did not have sufficient statistical power to detect differences in survival to hospital discharge [67]. The second was undertaken in Toronto, Canada and was an amiodarone versus lidocaine trial [68].

Patients who received amiodarone were significantly more likely to survive to hospital admission than those who received lidocaine, 22.8% versus 12% respectively (p=0.009). The adjusted OR for survival to hospital admission in the amiodarone group when compared with the lidocaine group was 2.17 (95%CI: 1.21-3.83). Additionally, there have been several other studies which document consistent improvements in defibrillation response post amiodarone administration [69-71]. There was little further evidence to support or refute the use of amiodarone before publication of the 2010 ILCOR recommendations and therefore it was left unchanged. However, all amiodarone studies up to this point had been undertaken while using the triple shock strategy [10] and therefore it may be beneficial to re-evaluate the use of amiodarone in combination with a single shock strategy.

The use of atropine was removed from ILCOR guidelines in 2005. It had previously been administered to patients in asystole or low rate PEA. This was as a result of various in-hospital [72, 73] and out-of-hospital studies [74-76] showing no consistent benefits of atropine administration in this cohort of patients. There was no further evidence for the use of atropine in cardiac arrest patients. Consequently 2010 recommendations regarding atropine use remained consistent with those of 2005.

Differences in Policy

Once finalised the ILCOR treatment recommendations are disseminated to various national / multi-national bodies that use them as a base to construct more detailed individual guidelines, such as those of the AHA [77], ERC [78] and The Australian Resuscitation Council (ARC) [79]. These guidelines are then disseminated to their corresponding members and the process continues ending with local trusts and services. It is at this point guidelines become incorporated into local systems and practice.

Guidelines produced by the national / multi-national or subsequent bodies are consistent with CoSTR, however are more detailed and take various other factors into account; including geographic, economic and system differences. ILCOR regard this as a necessary process; hence the term ‘consensus’, to indicate the understanding that local factors must impact on practice [1]. Some examples of this include: In 2005 The ERC [78] implemented the CAB approach, omitting rescue breaths, whereas ILCOR [6] maintained the ABC approach until 2010 [80]; The AHA did not remove atropine in 2005 [77] as per ILCOR; In 2010 The AHA advocates the use of vasopressin as a substitute for the first or second dose of epinephrine in cardiac arrest [81], which is not a practice indicated by ILCOR; The ARC and New Zealand Resuscitation Council (NZRC) did not implement the single shock strategy until post 2010 ILCOR recommendations [82], whereas ILCOR recommended this in 2005.

The QAS formulate and follow their own Clinical Practice Guidelines (CPGs), Clinical Practice Procedures (CPPs) and Drug Therapy Protocols (DTPs). These form the QAS Clinical Practice Manual (CPM), a guide informing patient care for all QAS practitioners. Resuscitation related aspects of CPGs, CPPs and DTPs are governed by ARC guidelines and produced in collaboration with the NZRC. These are based on ILCOR treatment recommendations.

QAS CPGs, CPPs and DTPs contain greater detail of management than ARC guidelines, in order to address Queensland specific issues. An example of this is within the Adult Resuscitation CPG [83] where it was first stipulated that an ETT must not be introduced (unless LMA failure) in the first 10 minutes of resuscitation. A further example is within an updated Adult Resuscitation CPG [84] which stipulates that when there are two officers only on scene, BLS procedures only are to be undertaken (unless glottic foreign body is suspected) for the first six minutes of resuscitation. These were both introduced to allow full focus on the deliverance of high-quality chest compressions and appropriate defibrillation, with minimal distractions.

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Appendix F: Search Strategy

A literature search to identify strategies (that have had an evaluation process undertaken 2007-2017) that may be used by paramedics when resuscitating adult (18years+) patients in cardiac arrest from cardiac aetiology in the out-of-hospital environment.

Databases:

Medline - MESH terms and keywords searched
Cinahl - Major headings and keywords searched
Informit - Keywords searched
Scopus - Keywords searched

Medline MESH terms:

5 concepts will be searched linked by 'AND'

Concept 1: Incident

Heart arrest (exploded) - includes out-of-hospital cardiac arrest; death, sudden, cardiac,
ventricular fibrillation (exploded)

Concept 2: Environment

Ambulances (exploded)
Emergency medical technicians (exploded)
Emergency medical services (focus)

Concept 3: Resuscitation attempt

Cardiopulmonary resuscitation (exploded) - includes advanced cardiac life support
Heart massage (exploded)

Concept 4: Strategy

Equipment and supplies (exploded)

Concept 5: Measurable Outcome

Survival rate (exploded)
Treatment outcome (exploded) includes treatment failure
Fatal outcome (exploded)

Cinahl Major headings (MH):

Concept 1: Incident

Heart arrest (exploded)
Death, sudden, cardiac (MC)
Ventricular fibrillation (MC)

Concept 2: Environment

Emergency Medical Services (MC)
Transportation of patients (explode)
Emergency medical technicians (MC)
Prehospital care (MC)

Concept 3: Subject to identify

Resuscitation (MC)
Heart massage (MC)
Resuscitation, cardiopulmonary (MC)
Advanced cardiac life support (MC)

Concept 4: Strategy

Equipment and supplies (explode)

Concept 5: Measurable Outcome

Treatment outcomes (explode)
Prognosis (MC)

Keywords:

Concept 1: Incident

asystole* OR "cardiac arrest" OR "cardiac arrests" OR "cardiopulmonary arrest" OR "cardiopulmonary arrests" OR "cardio pulmonary arrest" OR "cardio pulmonary arrests" OR "cardio-pulmonary arrest" OR "cardio-pulmonary arrests" OR "heart arrest" OR "heart arrests" OR "ventricular fibrillation" OR "ventricular fibrillations" OR VF* OR "electromechanical dissociation" OR "electromechanical dissociations" OR EMD* OR PEA* OR "pulseless" OR "ventricular standstill" OR OHCA* OR OOHCA* OR "sudden death" OR "sudden deaths" OR "sudden cardiac death" OR "sudden cardiac deaths"

Concept 2: Environment

"emergency medical service" OR "emergency medical services" OR EMS* OR ambulance* OR "emergency health service" OR "emergency health services" OR "emergency mobile unit" OR "emergency mobile units" OR "out of hospital" OR "out-of-hospital" OR "pre hospital" OR "pre hospitals" OR "pre-hospital" OR "pre-hospitals" OR prehospital* OR "emergency medical technician" OR "emergency medical technicians" OR "emergency medicine technician" OR "emergency medicine technicians" OR EMT* OR paramedic* OR "emergency medicine service" OR "emergency medicine services" OR "transportation of patient" OR "transportation of patients" OR "emergency care" OR "emergency cares"

Concept 3: Resuscitation

resuscita* OR "basic life support" OR "basic cardiac life support" OR BCLS* OR BLS* OR "advanced life support" OR "advanced cardiac life support" OR ALS* OR ACLS* OR CPR* OR "chest compressions" OR "heart massage"

Concept 4: Subject to identify

treatment* OR therapeutic* OR method* OR strategy OR strategies OR initiative* OR device* OR equipment* OR instrument* OR apparatus OR product* OR therapy OR therapies OR inventory OR inventories

Concept 5: Measurable outcome

surviv* OR prognos* OR outcome* OR result* OR "treatment effect" OR "treatment effects" OR evaluat* OR "treatment failure" OR "treatment success" OR "treatment successes" OR "treatment effectiveness" OR "treatment efficacy" OR "treatment failures" OR "return of spontaneous circulation" OR ROSC* OR "return of circulation" OR "return of spontaneous output" OR "return of output"

Appendix G: Ethics and approvals

Queensland Health HREC approval

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Public Health Act approval

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James Cook University ethics approval

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Appendix H: Data sources and variables

QAS OHCA Registry (case identifying dataset)

The QAS cardiac arrest registry is a purposive collection incorporating routine administrative and clinical data which prospectively collects purpose designed data. It was established in 1999 and has since developed in size (cases and variables) and completeness. In 2007 the collection system became largely digital, making records easier to access retrospectively.

It has 2 sources of information: 1) eARFs / DCARF and 2) Computer aided dispatch (CAD) system. All cases of cardiac arrest are identified by completion of a Death and Cardiac Arrest Report Form (DCARF) by QAS paramedics. In order to identify cases where a DCARF is not completed, a reconciliation process takes place whereby all eARFs are searched for key words. Those identified are then manually searched for evidence of cardiac arrest. These cases are then compiled into the cardiac arrest database. A thorough data cleaning process is undertaken. This identifies conflicting / inaccurate information within the dataset and allows this to be rectified. This cleaning process ensures the data is as complete and accurate as possible, in a format suitable for analysis.

In cases where multiple crews are in attendance or multiple journeys are undertaken in QAS care for the same event of cardiac arrest eg. acute transport followed by an IHT, duplicate cases may be formed. These are searched for and identified throughout the collation and cleaning processes. See QAS cardiac arrest registry coding manual for full definitions and methods [1].

The following table shows the variables provided by the QAS OHCA Registry:

Name	Type	Description
eARF	N	Electronic ambulance report from number (eARF) - The number independent to each identified OHCA
CARNumber	N	A number independent to each case of OHCA
Year	C	Year of case
Quarter	C	Year quarter
Month	C	Month of case
DayOfWeek	C	Day of week of case
CaseDate	D	Case date
Gender	C	Gender
BirthDate	D	Patient’s date of birth
AgeYears	N	Patient age (not necessarily calculated from birth date)
InitialRhythm	C	The initial cardiac rhythm recorded
CaseClassification	C	Identifies if the patient was dead on arrival (DOA), an inevitable death or a resuscitation attempt.
Aetiology	C	Presumed aetiology
WitnessedArrest	C	Identifies who witnessed the OHCA
BystanderCPR	C	Identifies if bystander CPR was undertaken and if it was effective
ChestCompression	C	Identifies if QAS undertook chest compressions
Outcome	C	Identifies the patient outcome at the end of QAS care
TimeReceived	TD	The date and time the call was received by QAS
TimeAtScene	TD	The date and time the first QAS resource was on scene
ResponseInterval	N	The time interval between TimeReceived and TimeAt Scene
TimeAtPatient	TD	The time and date the first QAS resource arrives at the patient’s side
TimeFirstIV	TD	The time and date the first IV is attempted (successful or otherwise)
TimeFirstDrug	TD	The time and date the first cardiac arrest specific drug is administered

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ICPAttended	C	To identify the presence of an Intensive/Critical Care Paramedic (I/CCP) in attendance
PreQASDefibType	C	To identify the presence of a defibrillator before QAS arrival
PreQASShocks	N	The number of shocks delivered before QAS arrival
QASDefibType	C	The type of defibrillator used by QAS
QASShocks	N	The total number of shocks delivered by QAS
TimeFirstShock	TD	The date and time the first shock was delivered
TimeFirstIntubation	TD	The time and date the first intubation attempt occurred (successful or otherwise)
FromLocationType	C	To identify the type of location at which the OHCA occurred
DestinationType	C	To identify the type of destination the patients was transported to
Destination	F	Destination address
DestStreetType	C	Destination street type
DestSuburb	C	Destination suburb
DestPostCode	C	Destination postcode
FromSuburb	C	Suburb of scene
FromPostCode	N	Postcode of scene
QASRegion	C	QAS Region
QASLASN	C	QAS Local Ambulance Service Network (LASN)
Case Nature	C	Case nature
ECGAttached	C	ECG attached submitted by paramedics
DCARFAttached	C	DCARF completed for case
Shocked	C	To identify patients that were shocked
Intubated	C	To identify successful intubation
LMA	C	To identify successful LMA placement
TimeFirstLMA	TD	The time and date the first LMA attempt occurred (successful or otherwise)
Cannulated	C	To identify successful IV/IO cannulation
Adrenaline	C	To identify successful IV/IO adrenaline administration

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OfficerLevel	C	To identify the most senior clinical officer in attendance
QASSkillSet	C	To identify the skill set of the most senior clinical officer in attendance
PatientSuburb	C	The patient's residential suburb
PatientPostCode	N	The patient's residential postcode
QASStation	C	QAS station (primary crew)
AircraftCase	C	To identify transport by aircraft
DNROrder	C	To identify the presence of a Do Not Resuscitate (DNR) order

N – numerical; C – categorical; T – time; D – date; F – free text

Queensland Hospital Admitted Patient Data Collection (QHAPDC)

The QHAPDC captures all admitted patient separations from public and private hospitals in Queensland. A separation may be formal, such as discharge, transfer or death; or statistical, such as when patients change from one care type to another within the same hospital (episode change) eg. acute care to maintenance.

Each hospital submits the required data items electronically using specific software. Hospitals must ensure that data are of high quality. Data is collected monthly and finalised on a financial year basis. See QHAPDC coding manual for full definitions and methods [2].

The following table shows the variables provided by the QHAPDC:

Name	Type	Description
SepID	N	Unique separation identifier
Birth_date	D	Patient's month and year of birth
Gender	C	Gender
Hospital	C	Hospital name
PD	C	Primary diagnosis code
OD_1	C	Other diagnosis code
OD_2	C	Other diagnosis code
Discharge_status	C	Discharge status
Admission_date	D	Admission month and year
Discharge_date	D	Discharge month and year
LOS	N	Length of stay in days
Postcode	N	Patient's residential postcode
State	C	Patient's residential state

N – numerical; C – categorical; D – date

Registrar General (RG) Death Registry

The RG Death Registry captures all deaths in Australia.

The following table shows the variables provided by the RG Death Registry:

Name	Type	Description
Person_ID	N	Unique person identifying number
Link_status	C	Identifies if case is linked to QHAPDC
Date_of_death	D	Month and year of Death
Days	N	For QAS/QHAPDC linked cases - number of days between hospital discharge date and date of death For QAS/QHAPDC unlinked cases - number of days between QAS date and date of death
Postcode	N	Patient's residential postcode

N – numerical; C – categorical; D – date;

References

1. Queensland Ambulance Service Cardiac Outcomes Registry - Coding Manual.
2. Queensland Hospital Admitted Patient Data Collection (QHAPDC) Manual 2015-2016 Version 1.0. 2015.

Appendix I: Data management

Variables (additional details)

Gender – This was manually constructed firstly using QAS recorded gender and overridden by QHAPDC recordings where matched and contradictory. 1 case changed from indeterminate to female, 21 were changed from male to female, 3 changed from indeterminate to male, 34 were changed from female to male and 1 case was recorded as male and female in the 2 QHAPDC records, so was left as female (as per QAS recording). The gender for 32 cases remained unknown.

Age – This was manually constructed firstly using QAS recorded information and overridden by QHAPDC recordings where matched and contradictory. Within QAS records, age and birth date are collected independently and are not always congruent. Age was present more often than birth date so in cases that were not linked with QHAPDC, age was taken as the dominant variable and birth date was only used to calculate age if age was not present. There were 2 cases which had no age recorded, but the QAS birth date was recorded as in the future (2021 and 2018). This was assumed to be a clerical error and changed to 1921 and 1928 respectively. Note - QHAPDC only provides birth date in month and year format. In cases where QAS and QHAPDC were successfully linked and birth dates were contradictory (in part or whole), the day of the 1st was allocated to the birth date, for the purpose of calculating age.

Discharge Status – This was manually constructed using the last discharge status recorded chronologically, the order of which was determined by separation ID variable. In some cases, inaccurate recording of dates / times by hospital staff may have led to incorrect crossover and subsequent incorrect allocation of separation ID to admissions. Therefore, if a previous discharge status was logically the last (died or discharged home/ usual residence) this was taken as the final. In cases where 2 or more logically last discharge status' were recorded, the one deemed as most final (ie. died in hospital) was allocated as the final discharge status.

Number of days until death – For linked QAS/QHAPDC cases this variable represents the number of days between QHAPDC discharge date and date of death and for non-linked QAS/QHAPDC cases the ‘FinalDays’ variable represents the recoded number of days between QAS case date and date of death. The origin of this variable is the Days variable as provided by the RG Death Registry data.

There were a total of 3157 cases with a negative Days variable (3156 in working dataset post appropriate exclusion of cases). The Data Linkage Unit reported that 2034 (of the original 3157) had a range recorded as a date of death which was the likely cause of the negative values. The remaining 1123 were likely due to clerical error.

The breakdown of case classifications for these was investigated to further inform accurate recoding. This showed: 1667 DOA, 1268 inevitable death and 221 resuscitation attempts. All of the cases coded by QAS as DOA or inevitable death (2935) were recoded with a FinalDays variable of 0.

The remaining 221 cases with a negative ‘Days’ variable included the following breakdowns: 213 recorded as -1 days; 2 recorded as -2 days; 1 recorded as -3 days; 1 recorded as -5 days; 2 recorded as -7 days; 1 recorded as -51 days; and 1 recorded as -365 days. The QAS outcome was looked at for all cases with a 2-day or more discrepancy and in all cases was one involving no ROSC, therefore they were all allocated 0. The 213 cases which had a ‘Days’ variable of -1 were assumed to be due to clerical error of date recording and therefore also recoded as 0.

Additionally, of the original 221 cases that had a resuscitation attempt, 69 were linked with QHAPDC demonstrating hospital admission. As a method of quality assurance, the ‘FinalDischargeStatus’ of these was examined. This showed 65 cases ‘Died in hospital’ so we can be sure that the recode to 0 in ‘FinalDays’ is as accurate as can be as they were never discharged. The remaining 4 cases had an alternative final discharge status - 1 was recorded as discharged to a residential age care facility, 1 as an episode change and 2 as discharged home/usual residence. The ‘FinalDays’ variable for these 4 cases was left as 0 as there was no further information available to improve accuracy.

Cases linked to RG Death Registry but not linked to QHAPDC:
There were 49 cases not linked with QHAPDC with a RG Death Registry 'Days' variable ≥2 (indicating it is most likely they went to hospital) and coded contradictorily twice by QAS: 1) QAS outcome indicating a resuscitation attempt was either not made or stopped before hospital (DOA, no ROSC died at scene, no ROSC died in transport, ROSC died at scene, ROSC died in transport); and 2) No destination recorded by QAS (destination variable missing, 0 or >241). This therefore highlighted probable error which was likely as a result of the date range being used to estimate date of death or clerical error so were changed to a value of '0' in 'FinalDays'. This was not done in cases that were linked with QHAPDC, as the patients from these cases were admitted and therefore overrules a QAS classification indicating a patient did not survive to hospital.

Length of Stay – The sum of each length of stay for every QHAPDC entry (up to the one deemed as the final one), linked with that case.

Days To Death From Case Date – Represents the total number of days from case date to death. This variable was constructed, using the entry for FinalDays for those cases not linked with QHAPDC and FinalDays + Total_LOS for those cases linked with QHAPDC.

Cases not linked with RG Death Registry:
Cases linked with QHAPDC but not with RG Death Registry were analysed further to inform the most likely date of death. Of the 1285 cases (linked with QHAPDC only), 55 had a FinalDischargeStatus of 'Died in hospital'. It was assumed that these patients were unsuccessfully linked with their death records and they died on their last day in hospital therefore they were allocated their Total_LOS value as their DaysToDeathFromCaseDate value.

The 'FinalDischargeStatus' for the remaining 1230 cases that were linked with QHAPDC but not RG Death Registry were: correctional facility (2); discharged at own risk (13); episode change (103); home/usual residence (707); other (2); other health care establishment (9); other hospital – not contract (29); residential aged care facility (4); transfer to another hospital (361). It is known that these patients survived to either hospital admission or discharge but nothing further regarding outcome can be determined. These patients were allocated and are represented by a ‘DaysToDeathFromCaseDate’ are labelled as ‘Admitted but unknown further’ if transfer to another hospital, other hospital not contract, episode change or other; or labelled as ‘Discharged but unknown further’ if ‘FinalDischargeStatus’ is home/usual residence, other health care establishment, residential aged care service, discharged at own risk or correctional facility.

It is possible that cases unsuccessfully linked to the RG Death Registry represent a false negative, however most likely, the patients that were discharged are still alive, which was assumed.

Cases not linked to QHAPDC or RG Death Registry were analysed further to inform the most likely date of death. Of the 1947 cases not linked to QHAPDC or RG Death Registry, 1217 had QAS recorded outcomes indicating death on that day (DOA (826); no ROSC died at scene (360); no ROSC died in transport (13); ROSC died at scene (14); or ROSC died in transport (4)). It can be assumed that these patients died on the case date so were allocated a value of 0 for the ‘DaysToDeathFromCaseDate’ variable.

The QAS outcome of the remaining 730 cases that were not linked with QHAPDC or RG Death Registry were: no ROSC no ROSC at hospital (151); ROSC on hospital arrival (556); and ROSC no ROSC at hospital (23). These patients are either: 1) still alive (and were either not admitted or had unsuccessful linkage to QHAPDC); or 2) died in ED with unsuccessful linkage to RG Death Registry records; or 3) died post admission with unsuccessful linkage to QHAPDC or RG Death Registry records. These patients were labelled as ‘Unknown’.

Initial Shockable Status – This represents the shockable status of the first cardiac arrest rhythm detected by QAS. This was constructed from the QAS variable InitialRhythm. The allocation ‘Shockable’ was applied to those cases coded as ‘vent fib fine’, ‘vent fib course’, ‘vent tach’. The allocation ‘Non-shockable’ was applied to those cases coded as ‘asystole’, ‘PEA’, ‘agonal dying heart’. The allocation ‘Unknown’ was applied to those cases coded as ‘ECG not taken’, ‘other’ or ‘unknown’.

Dichotomous outcome variables

The dichotomous outcome variables (yes/no) were calculated in this order:

1) Resuscitation (yes/no) – Refers to cases in which a resuscitation attempt was made by QAS. Constructed firstly using the QAS variable case classification and allocating ‘Yes’ to all cases coded as resuscitation attempt. Cases that did not have a resuscitation attempt (DOA, inevitable death) were allocated ‘No’. There were 5 cases in which QAS case classification indicated the patient was not resuscitated but the QAS outcome indicated a resuscitation attempt was made (1 x DOA coded as ROSC on hospital arrival, 4 x inevitable death coded as ROSC (2 x sustained to hospital and 2 x not sustained to hospital)) and there were 7 cases in which QAS case classification indicated the patient was resuscitated but the QAS outcome indicated a resuscitation attempt was not made (resuscitation attempt coded as DOA). In these cases, further evidence of a resuscitation attempt was sought (ie evidence of IV access, drug administration, defibrillation or intubation), the result of which being the overriding factor for the final ‘Resuscitation’ allocation – 5 cases (4 x inevitable death and 1 x DOA) were changed from a ‘No’ to a ‘Yes’ allocation. The remaining cases all had further evidence that a resuscitation attempt was made, so were not changed.

2) AnyPreHospitalROSC (Yes/no) – Refers to cases in which any pre-hospital ROSC was achieved. Firstly, cases that did not receive a resuscitation attempt were allocated ‘No’. Cases with QAS outcome as having any period of ROSC (ROSC on hospital arrival, ROSC died at scene, ROSC died in transport or ROSC no ROSC at hospital) were allocated ‘Yes”. Cases with QAS outcome as having no period of ROSC (DOA, no ROSC died at scene, no ROSC died in transport) were allocated ‘No’. There was 1 case that did not have a QAS outcome, this was allocated ‘No’. This resulted in 4892 cases allocated with ‘Yes’ and 27427 cases with ‘No’.

3) ROSCToHospital (Yes/no) – Refers to cases in which pre-hospital ROSC was achieved and sustained to hospital. Firstly, cases allocated as ‘No’ for the variable ‘AnyPreHospitalROSC’ were allocated ‘No’. Of the remaining cases, those classified as ROSC to hospital within QAS outcome were allocated ‘Yes’. This was applicable in 4175 cases. Additionally, a further case was allocated ‘Yes’ for this variable (see explanation under ‘SurvivalToAdmission’ variable).

4) ROSCinED (Yes/no) – Refers to cases in which ROSC was achieved in ED (ie. the patient did not have ROSC on ED arrival). Of the cases allocated as ‘No’ for the variable ‘ROSCToHospital’, it was assumed that ROSC was achieved in ED if it was successfully linked with QHAPDC and as such was allocated ‘Yes’. This was the case in 1261 cases. A further 24 cases were allocated ‘Yes’ for this variable (see explanation under ‘SurvivalToAdmission’ variable). The remaining cases were allocated ‘No’.

5) AnyROSC (Yes/no) - Refers to cases in which an episode of ROSC was achieved either before or in ED. If the patient had a ‘Yes’ allocation for either ‘AnyPreHospitalROSC’ or ‘ROSCinED’, it was allocated ‘Yes’. This applied to 5960 cases (217 of which had ‘Yes’ for both ‘AnyPreHospitalROSC’ and ‘ROSCinED’ meaning they had an episode of pre-hospital ROSC which was not sustained to ED, then another episode of ROSC in ED).

6) ROSCTo_AtHospital (Yes/no) - Refers to cases in which ROSC was achieved either out of hospital and maintained to ED, or in ED. If the patients had a ‘Yes’ allocation for either ‘ROSCToHospital’ or ‘ROSCinED’, it was allocated ‘Yes’. This applied to 5436 cases. A further 24 cases were allocated ‘Yes’ for this variable (see explanation under ‘SurvivalToAdmission’ variable)

7) NotDeadAtEDArrival (Yes/no) - Refers to cases in which recognition of death had not occurred at hospital arrival (ie. either ROSCToHospital was ‘Yes’ or resus was still underway at hospital arrival). Firstly, cases allocated a ‘Yes’ for the variable ‘ROSCToHospital’ were also allocated ‘Yes’. Of the remaining cases, those with a QAS outcome indicating no pre-hospital death (ie. No ROSC no ROSC at hospital, ROSC on hospital arrival, ROSC no ROSC at hospital) were allocated ‘Yes’ and

those with a QAS outcome indicating a pre-hospital death (ie. DOA, no ROSC died at scene, no ROSC died in transport, ROSC died at scene, ROSC died in transport) were allocated ‘No’. This was overridden to ‘Yes’ if the case was linked with QHAPDC, which occurred in 172 cases. There was 1 case that did not have a QAS outcome, but was recorded as transported so was allocated ‘Yes’.

8) SurvivalToAdmission (Yes/no) – Refers to cases in which the patient survived to hospital admission. Firstly, cases successfully linked to QHAPDC were allocated ‘Yes’ (4324 cases). Of the cases not linked with QHAPDC, if the ‘DaysToDeathFromCaseDate’ variable was ≥2 the case was also allocated ‘Yes’ (assumed admission). This applied to a further 246 cases. Of these, 25 originally had ‘No’ allocated for ‘ROSCTo_AtHospital’, which is contradictory (it was assumed that if the patient was admitted, ROSC was also achieved beforehand), so was changed to ‘Yes’. Of those 25, 24 had no evidence of pre-hospital ROSC, so it was assumed the ROSC occurred in ED and their ROSCinED allocation was also changed to ’Yes’. The remaining 1 had evidence of pre-hospital ROSC but no evidence if it was sustained or unsustained. It was assumed to be sustained, so had its ROSCToHospital allocation changed to ‘Yes’. 555 cases SurvivalToAdmission status was unknown due to unsuccessful linkage with either QHAPDC or RG Death Registry - this is clearly an error with linkage as all patients should theoretically be linked to either or both.

9) SurvivalToDischarge (Yes/no) – Refers to cases in which the patient survived to hospital discharge. Firstly, cases allocated ‘No’ for SurvivalToAdmission, were allocated ‘No’ for SurvivalToDischarge. ‘Yes’ was allocated if ‘FinalDischargeStatusNumeric’ was coded as ‘home/usual residence’, ‘residential age care service’, ‘other health care establishment’, ‘non-return from leave’, ‘discharged at own risk’ or ‘correctional facility’. ‘No’ was allocated if ‘FinalDischargeStatusNumeric’ was coded as ‘died in hospital’. The SurvivalToDischarge status was unknown if: ‘FinalDischargeStatusNumeric’ was coded as ‘transferred to another hospital’, ‘episode change’, ’other’, ‘other hospital not contract’; the case gained a positive SurvivalToAdmission status because DaysToDeathFromCaseDate≥2, although not linked with QHAPDC; or if the case

had a SurvivalToAdmission status of unknown. A ‘No’ allocation was applied in all other cases.

10) SurvivedEvent (Yes/no) – Refers to cases in which the patient either survived to hospital discharge OR to 10 days or more. Firstly, cases with SurvivalToAdmission status as ‘No’ or unknown, remained as such for SurvivedEvent. Of the cases allocated ‘Yes’ for SurvivalToAdmission, ‘Yes’ was allocated for SurvivedEvent if: 1) The patient was allocated ‘Yes’ for SurvivalToDischarge; 2) The entry for ‘DaysToDeathFromCaseDate’ ≥10; or 3) The case was linked to QHAPDC, but not RG Death Registry, with no conclusive outcome noted (therefore presumed still alive).

11) SurvivalTo1Day – Refers to cases in which the patient survived to 1 day or more. All cases allocated ‘No’ for ROSCTo_AtHospital were also allocated ‘No’ for ‘SurvivalTo1Day’. Of the cases allocated ‘Yes’ for ROSCTo_AtHospital, those with 1 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. There were 1230 cases within this group that were not linked to RG Death Registry but linked to QHAPDC with the final discharge status not indicating death. As previously described these patients either 1) are still alive; or 2) died with unsuccessful linkage to RG Death Registry records. It is known that these patients survived to hospital admission but nothing further regarding outcome can be determined. These were allocated a status of ‘Unknown past admission’. 555 cases were not linked to either QHAPDC or RG Death Registry which indicates an error with linkage as they should be linked with one or both (unless they were discharged or absconded from ED and are still alive – a very unlikely scenario). These cases were allocated an ‘Unknown – not linked’. The ‘Unknown past admission’ and ‘Unknown – not linked’ allocations remained the same for all subsequent length of survival outcomes.

12) SurvivalTo2Days - Refers to cases in which the patient survived to 2 days or more. All cases allocated ‘No’ for SurvivalTo1Day were also allocated ‘No’ for ‘SurvivalTo2Days’. Of the cases allocated ‘Yes’ for SurvivalTo1Day, those with 2 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. All remaining cases were allocated ‘No’.

13) SurvivalTo30Days - Refers to cases in which the patient survived to 30 days or more. All cases allocated ‘No’ for SurvivalTo2Days were also allocated ‘No’ for ‘SurvivalTo30Days’. Of the cases allocated ‘Yes’ for SurvivalTo2Days, those with 30 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. All remaining cases were allocated ‘No’.

14) SurvivalTo60Days - Refers to cases in which the patient survived to 60 days or more. All cases allocated ‘No’ for SurvivalTo30Days were also allocated ‘No’ for ‘SurvivalTo60Days’. Of the cases allocated ‘Yes’ for SurvivalTo30Days, those with 60 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. All remaining cases were allocated ‘No’.

15) SurvivalTo180Days - Refers to cases in which the patient survived to 180 days or more. All cases allocated ‘No’ for SurvivalTo60Days were also allocated ‘No’ for ‘SurvivalTo180Days’. Of the cases allocated ‘Yes’ for SurvivalTo60Days, those with 180 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. All remaining cases were allocated ‘No’.

16) SurvivalTo365Days - Refers to cases in which the patient survived to 365 days or more. All cases allocated ‘No’ for SurvivalTo180Days were also allocated ‘No’ for ‘SurvivalTo365Days’. Of the cases allocated ‘Yes’ for SurvivalTo180Days, those with 365 or more in ‘DaysToDeathFromCaseDate’ variable were allocated ‘Yes’. All remaining cases were allocated ‘No’.

17) Sequential Pre-hospital Outcomes – The categories within this variable are mutually exclusive pre-hospital outcomes. They show the final chronological outcome reached by the patient. There are 4 categories, as follows: 1) No resuscitation attempt; 2) Resuscitation attempt, no pre-hospital ROSC; 3) Resuscitation attempt, pre-hospital ROSC but not to ED; 4) Resuscitation attempt, pre-hospital ROSC to ED.

18) Sequential Hospital Outcomes - The categories within this variable are mutually exclusive long-term outcomes. They show the final chronological outcome reached

by the patient. The initial population for this variable is all patients who had pre-hospital ROSC to ED and/or those who had ROSC in ED (those with a 'Yes' allocation for ROSCTo_AtHospital). This are 4 main categories, as follows: 1) No survival to admission; 2) Survival to admission, but not to 30 days; 3) Survival to 30 days, but not to 365 days; 4) Survival to 365 days or more. Cases not included in the initial population are within the category labelled N/A and cases in which an outcome past ROSC at ED cannot be determined (not linked to QHAPDC or RG Death Registry – representing a practically impossible situation) are within the category labelled U/K.

Assumptions

Cases linked to QHAPDC, but not the RG Death Registry and had a final discharge status of 'died in hospital' were assumed to have died on their final day in hospital – These cases had their DaysToDeathFromCaseDate entry calculated accordingly.

Cases linked to QHAPDC, but not the RG Death Registry and had a final discharge status suggesting discharge alive were assumed to be still alive.

Cases not successfully linked to either QHAPDC or RG Death Registry, were excluded from analyses past hospital arrival – This lack of linkage was deemed to be due to linkage problems as OHCA without hospital admission and/or death is truly a very unlikely scenario. It is only possible if the patient has been resuscitated successfully by QAS and not transported or transported and discharged from ED so not admitted. Alternatively, it is possible that the patient was transferred from ED to a facility not in QHAPDC and has not yet died.

Cases with ROSC to/at ED, were not linked with QHAPDC but were linked with RG Death Registry with the number of days from case date to death greater than or equal to 2, were assumed to have been admitted.

Cases that did not have ROSC to ED (according to QAS) but were linked to QHAPDC, were assumed to have ROSC at ED.

Limitations of the linkage and merging methods

1. QAS duplicates not linked to RG Death Registry would not have been identified by the Data Linkage Unit.
2. QAS cases not linked with QHAPDC cannot have their age and gender variables identified as incorrect or correct, as per those linked with QHAPDC.
3. There were 5 cases in which were originally coded with an outcome of No-Resus but based on further evidence within QAS data were subsequently changed to include a resuscitation attempt. This change was made post linkage, so these cases did not have linkage with QHAPDC and RG Death Registry attempted.
4. Time lapses in ED were not accounted for when calculating the 'DaysToDeathFromCaseDate' variable for cases successfully linked and merged with QHAPDC records. It is possible the patient may have had a cardiac arrest within a few hours before midnight and been admitted the following day (after midnight), in which case the 'Total_LOS' variable would be inaccurate by 1 day and therefore so would the respective 'DaysToDeathFromCaseDate'entry.
5. The 'Days' variable (from RG Death Registry) represents the number of days between QHAPDC discharge date and date of death for linked QAS/QHAPDC cases and between QAS case date and date of death for non-linked QAS/QHAPDC cases - This calculation was made only by date (not by time) so the variable actually represents the number of midnights the interval spans rather than full 24-hour periods eg. 2 days actually represents anywhere between >24 hours - <72hours.
6. The RG Death Registry sometimes has date of death recorded as a range. In these cases the 'days' variable is calculated using the first date in the range so if the QHAPDC discharge date / QAS case date is later than this, the 'days' variable will be a negative value. It is possible that cases with a 0 or positive 'Days' variable had this variable calculated using a range as a date of death and may therefore be inaccurate. The Data Linkage Unit reported that only 51 out of 25967 cases (initial linkage figure) with a 0 or positive 'Days' variable had a range recorded as date of death. Due to the small numbers identification of these cases was not undertaken, however further investigation of the data was. The Data Linkage Unit indicated that clerical error is common when recording dates.