“Revealing the Roadblocks in STEMI Management”

Timely STEMI Management over Total Ischaemic Time in Metropolitan, Regional and Rural Victoria.

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This thesis is submitted in total fulfilment of the requirements for a

Doctor of Philosophy with publication

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STATEMENT OF AUTHORSHIP

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma. No other person's work has been used without due acknowledgment in the main text of the thesis. This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

This thesis includes work by the author that has been published and manuscripts submitted or ready to submit as described in the text. The extent of contribution by co-authors of the publication and manuscripts is outlined in the following section “Statement of Contribution” for each paper.

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Lorelle Martin

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STATEMENT OF CONTRIBUTION FOR PAPER 1

***Title**: Australian STEMI patients currently meeting the updated European Society Cardiology (ESC) reperfusion target parameters and the impact on one-year outcomes* *(Manuscript ready to submit)*

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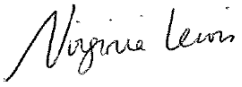
Virginia Lewis	**Overall contribution 7.5%** Concept and design of the study Analysis and interpretation of data Made critical revision to draft versions	
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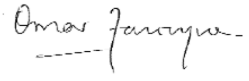
Omar Farouque	**Overall contribution 10%** Concept and design of the study Analysis and interpretation of data Made critical revision to draft versions	

STATEMENT OF CONTRIBUTION FOR PAPER 2

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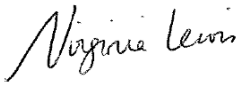
Virginia Lewis	**Overall contribution 5%** Concept and design of the study Analysis and interpretation of data Made critical revision to draft versions	
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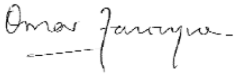
Omar Farouque	**Overall contribution 5%** Concept and design of the study Made critical revision to draft versions	

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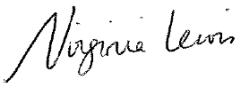
Virginia Lewis	**Overall contribution 15%** Concept and design of the study Analysis and interpretation of data Made critical revision to draft versions	
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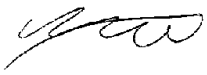
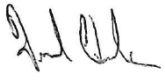
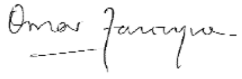
Dion Stub	**Overall contribution 2.5%** Concept and design of the study Facilitated data collection Made critical revision to draft versions	
David Clark	**Overall contribution 2.5%** Concept and design of the study Made critical revision to draft versions	
Omar Farouque	**Overall contribution 2.5%** Concept and design of the study Made critical revision to draft versions	

LIST OF ABBREVIATIONS

ACS:	Acute Coronary Syndrome
AHA:	American Heart Association
ALS:	Advanced Life Support
AV:	Ambulance Victoria
CCL:	Cardiac Catheterisation Laboratory
CENA:	College of Emergency Nursing Australasia
CHD:	Coronary Heart Disease
CSANZ:	Cardiac Society of Australia and New Zealand
CVD:	Cardiovascular Disease
DTBT:	Door to Balloon Time
DTNT:	Door to Needle Time
ECG:	Electrocardiogram
ED:	Emergency Department
ESC:	European Society of Cardiology
FMC:	First Medical Contact
GRACE:	Global Registry Acute Coronary Events
IHD:	Ischaemic Heart Disease
LBBB:	Left Bundle Branch Block
MICA:	Mobile Intensive Care Ambulance
NSTEMI:	Non-ST-segment Elevation Myocardial infarction
PAF:	Principal Axis Factoring
PCA:	Principal Component Analysis
PHN:	Pre-Hospital Notification
PHT:	Pre-Hospital Thrombolysis
PCI:	Percutaneous Coronary Intervention
STEMI:	ST-segment Elevation Myocardial Infarction
TDF:	Theoretical Domains Framework
TIMI:	Thrombolysis in Myocardial Infarction
UA:	Unstable Angina
VAS:	Visual Analogue Scale

DISSEMINATION OF FINDINGS

August 2016	**CSANZ published abstract** Mini-oral presentation: "*Pre-hospital delay for STEMI patients and the effect on total ischaemic time and health outcomes"*
September 2016	**Research Week:** La Trobe Research Showcase Accepted poster: *"Does mode of presentation to hospital in STEMI impact on total ischaemic time and health outcomes?"*
October 2016	**Research Week:** Austin Health Accepted poster: *"Does mode of presentation to hospital in STEMI impact on total ischaemic time and health outcomes?"*
May 2017	**EuroPCR *(sub-group analysis)*** Oral presentation: '*Patients with atrial fibrillation (AF) who present with STEMI have different baseline characteristics, clinical outcomes and logistic parameters'*
August 2018	**CSANZ published abstract** Oral presentation: *Are the new European Society of Cardiology (ESC) STEMI performance targets feasible? The proportion of achievement in performance targets using the new ESC STEMI guidelines compared to existing Australian guidelines, applied to a nine-year prospectively collected dataset".* **CSANZ published abstract** Accepted poster: *"Barriers to timely STEMI management as reported by paramedics and Triage nurses: a cross sectional study".*
August 2019	**CSANZ published abstract and prize winner *(sub-group analysis)*** Moderated poster: *"Differences in characteristics, performance targets and outcomes for men and women with STEMI at a large tertiary Australian hospital. (see appendix 1)*
October 2018	**ResearchFest Austin Health prize winner *(sub-group analysis)*** Accepted Poster: *"Differences in characteristics, performance targets and outcomes for men and women with STEMI at a large tertiary Australian hospital. (see appendix 1)*
May 2020	**EuroPCR** Accepted oral presentation: "*An analysis of time to electrocardiogram (ECG) and STEMI reperfusion target times: a single tertiary site prospective analysis"*

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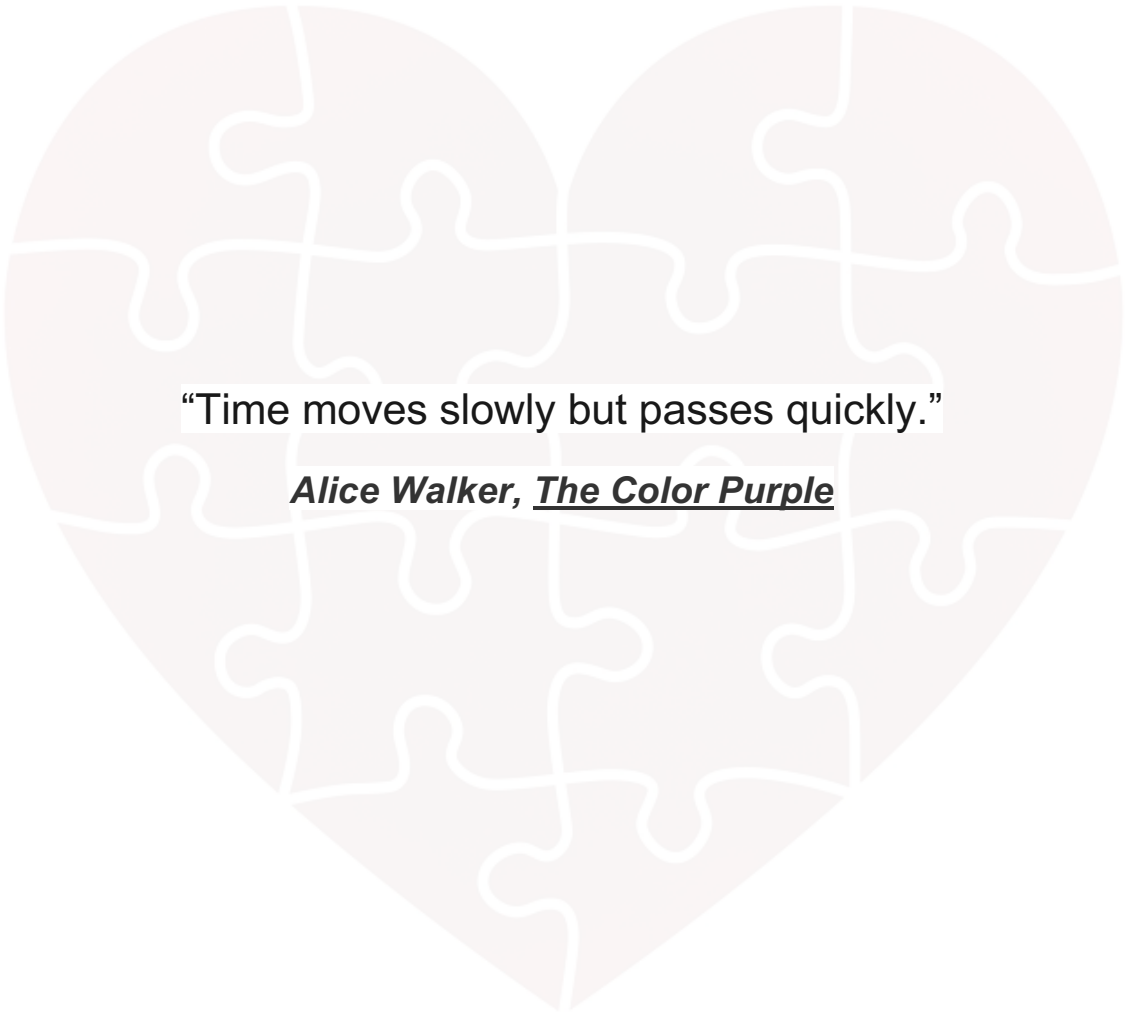

“Time moves slowly but passes quickly.”

Alice Walker, <u>The Color Purple</u>

ABSTRACT

Background

The management of ST-segment elevation myocardial infarction (STEMI) requires prompt diagnosis and reperfusion to restore epicardial blood flow. Guidelines advocate time parameters to expedite access to the cardiac catheterisation laboratory (CCL), with European guidelines recently diverging from existing Australian guidelines. Time to treatment targets are valuable in measuring performance, however, provide little understanding of the metrics of time delay over total ischemic time. Furthermore, the pivotal role and experiences of frontline clinicians in timely management as first medical contact (FMC) is largely overlooked in STEMI systems of care.

Aims

The aim of this thesis was to explore and describe STEMI management in relation to the recommended time parameters and the barriers and enablers to timely treatment, using three separate studies.

Methods

The three studies conducted used different methodologies. The first two studies analysed a large single site STEMI cohort, the third study surveyed frontline clinicians. Study I compared the achievement rate of Australian and European STEMI guidelines for a consecutive STEMI cohort, and applied Cox proportional hazard modelling to establish the impact European targets had on health outcomes. Study II utilised cubic smoothing splines and logistic regression to identify the optimal time parameters associated with the highest probability of achieving reperfusion targets STEMI management. Additionally, quantile regression identified the effect explanatory variables had on the same three components of care. Study III offered an online survey to paramedics and Emergency Nurses using descriptive statistics and exploratory factor analysis to identify frequently experienced barriers.

Results

Study I found European targets were difficult to achieve and revealed no impact on mortality at 12-months compared to existing Australian STEMI guidelines. Study II identified an ‘FMC-ECG’ time between 6-7 minutes or less, an ‘FMC-CCL’ time between 29-51 minutes or less, and a ‘symptom onset-FMC’ time between 99-108 minutes or less were associated with achieving reperfusion targets, depending on presentation mode. Quantile regression revealed several explanatory variables associated with influencing

time to treatment for all three components of care. Study III confirmed barriers were present for frontline clinicians but infrequently experienced, with the top two barriers identified as ‘lack of skills development’ and ‘lack of clinical feedback’. There were significant differences between professions and geographic location.

Conclusion

The combined findings from the studies indicated that mode and time of presentation, advanced age, gender, lack of skills/development and feedback mechanisms all presented challenges in the delivery of effective and efficient STEMI management. Robust system interventions, such as two-way communication to provide timely access to clinical expertise and establishing real-time feedback protocols that interface with existing processes of care could address some of these challenges.

CHAPTER ONE: INTRODUCTION

1.0 Chapter introduction

The following chapter will outline the thesis topic and define the cardiovascular condition of interest, ST-segment elevation myocardial infarction (STEMI). The prevalence, rate of mortality and cost of treating cardiovascular disease will be described, as will the current performance target guidelines for STEMI. Additionally, this chapter will introduce the study context, thesis rationale, research aims and specific research questions. An outline of the thesis structure will be provided, including a table of the published research and manuscripts under review or ready to submit to illustrate alignment with the research aims.

1.1 Definitions of CVD

Cardiovascular disease (CVD) is defined as all diseases of heart and blood vessels (Australian Institute of Health and Welfare., 2018). This definition includes coronary heart disease, stroke, heart failure and peripheral vascular disease. Coronary heart disease (CHD), also known as ischaemic heart disease (IHD), is the largest subset of CVD and is caused primarily by coronary atherosclerosis (Australian Institute of Health and Welfare., 2018). Acute coronary syndrome (ACS) refers to any group of acute clinical symptoms of myocardial ischaemia that are high-risk manifestations of coronary atherosclerosis. Categories of ACS range from unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), to ST-segment elevation myocardial infarction (STEMI) (Australian Institute of Health and Welfare., 2013). This thesis will focus exclusively on the subcategory STEMI.

1.2 Prevalence of CVD and IHD

In Australia 1.2 million people are reported to have CVD, accounting for 6% of the population (Australian Institute of Health and Welfare., 2019a). This percentage increases with age, with 26% of people aged 75 years and over reporting a CVD condition (Australian Institute of Health and Welfare., 2019a). In 2015-16, CVD accounted for 1.1 million episodes of hospital care as the principal diagnosis and/or additional diagnosis, representing 11% of all hospitalisations (Australian Bureau of Statisitics., 2019b).

In terms of the condition of interest, approximately 3% of the population reported having an IHD condition at some time in their lives (Australian Bureau of Statisitics., 2019b). In

the absence of reliable data measuring the incidence (or new cases) of IHD, it is estimated that over 500,000 Australians each year are investigated for acute chest pain in Emergency Departments (ED), but under 20% have a confirmed ACS diagnosis, with around 2-5% receiving a STEMI diagnosis (Chew et al., 2016). According to hospitalisation and mortality data, in 2016, there were an estimated 170 ACS events every day (Australian Institute of Health and Welfare., 2019a). Encouragingly, the rate of these ACS events has declined rapidly by 37% over the past 11 years (Australian Institute of Health and Welfare., 2019a).

1.3 Mortality rates of IHD and CVD

The single largest cause of mortality in Australia is IHD accounting for 17,533 (11.1%) of all deaths in 2018, and the subset of STEMI representing 7,322 (42%) of these deaths (Australian Bureau of Statisitics., 2019a). Both age and gender play large roles in the death rate of IHD. While the standardised death rate from IHD has decreased by 22.4% since 2009, IHD is still considered the most avoidable death for the age group between 45-74 years of age (Australian Bureau of Statisitics., 2019a). In 2017, the death rate from IHD for males and females under the age of 75 years was 292 and 87 deaths per 100,000 population respectively. This mortality rate dramatically increases over the age of 75 years with 2679 and 1992 deaths per 100,000 population for males and females respectively (Australian Institute of Health and Welfare., 2019a).

After adjusting for age, CVD death rates are higher for those living in remote areas and in low socioeconomic areas, with 135 deaths per 100,000 population, 1.4 times higher than metropolitan areas (Australian Institute of Health and Welfare., 2019a). This gap was similar for both males and females. This inequality is reported as a reflection of the higher proportion of Australia's First Peoples living in remote areas and lack of accessibility to health care for the remote area population as a whole (Australian Institute of Health and Welfare., 2019a).

1.4 Cost of treating CVD

The most recent report outlining total health care expenditure in Australia for 2015-16 states CVD was the second highest level of expenditure for any disease group, with an estimated cost of $10.4 billion or 9% of the allocated health care expenditure for Australia (Australian Institute of Health and Welfare., 2019b). More specifically, IHD accounted for 21% of the total expenditure of CVD, with services for hospitalised CVD patients

accounting for 38% of total CVD expenditure in 2015-16 (Australian Institute of Health and Welfare., 2019b).

1.5 Current STEMI performance target parameters

Guidelines for STEMI management recommend specific time-related target parameters for delivery of care from initial diagnosis through to epicardial reperfusion. The target parameter for time to diagnosis suggests no more than 10 minutes is taken from first medical contact (FMC) to 12-lead ECG for any patient presenting with acute chest pain suggestive of STEMI (Chew et al., 2016; Ibanez et al., 2018; O'Gara et al., 2013). The time to reperfusion target parameter is twofold and dependant on choice of reperfusion strategy. The first and preferred reperfusion strategy is primary percutaneous coronary intervention (primary PCI), and has a target parameter of no more than 90 minutes from FMC to balloon reperfusion. The second strategy if primary PCI is not available is fibrinolytic therapy, with a target parameter of no more than 30 minutes from FMC to intravenous administration of fibrinolysis (Chew et al., 2016; Ibanez et al., 2018; O'Gara et al., 2013). These time parameters are more commonly referred to as 'Door-ECG' time, 'Door-Balloon Time' (DTBT) and 'Door- Needle time" (DTNT) respectively.

The peak cardiology body of Australia, the Cardiac Society of Australia and New Zealand (CSANZ) (Chew et al., 2016), grades the time to diagnosis target parameter ('Door-ECG' time) as 'Strong' with an NHMRC level of evidence of IIIC; i.e., satisfactory comparative studies without controls. The time to reperfusion target parameters ('DTBT' and 'DTNT') are also graded as 'Strong' with a higher NHMRC level of evidence of IA; i.e., excellent systematic reviews of randomised control trials (National Health and Medical Research Council., 2016).

Another time parameter of STEMI management recognised in the literature is total ischemic time (O'Gara et al., 2013). This time parameter measures the total time taken from onset of symptoms to reperfusion of the culprit coronary artery. Total ischemic time takes into account the pre-hospital duration of myocardial ischemia and has shown to have a stronger correlation to infarct size and mortality (Eitel et al., 2010). Guidelines recommend that no longer than 210 minutes is taken from onset of symptoms to coronary reperfusion (O'Gara et al., 2013). As a metric of quality improvement this is an important target to reduce; however, it is a complex time parameter to improve. Total ischemic time measures not only the health seeking behaviour of the patient to make initial contact with health services, but the efficiency of hospital processes of care to diagnose, initiate and

deliver reperfusion strategies. Furthermore, the contemporary landscape of STEMI management has capacity to diagnose STEMI and initiate reperfusion services prior to hospital arrival. This pre-hospital system of care is not clearly measured in the international guidelines.

In 2017, this gap was addressed by the peak European cardiology body, the European Cardiac Society (ESC), by introducing explicit changes to how STEMI performance time was measured. Target time parameters expanded to include 'field' FMC for pre-hospital notification (PHN) of STEMI's diagnosed prior to hospital arrival. Furthermore, they reduced the target parameter of hospital diagnosed STEMI from 90 minutes to 60 minutes. The ESC guidelines also removed terminology such as DTBT or DTNT to clearly delineate the start of the FMC time parameter as either in the hospital setting or out in the community where a STEMI diagnosis could be made.

A summary of the aforementioned international guidelines displaying the similarities and differences is presented below in *Table 1* to provide a point of reference.

Table 1*: Summary of international guidelines for primary PCI.*

Time parameter	Time target (minutes)		
	Cardiac Society Australia and New Zealand	**American Heart Association**	**European Society Cardiology**
Symptom onset to reperfusion	within 12 hours	210	210
Door to ECG	10	10	10
Door to Balloon (all arrivals)	90	90	-
FMC to reperfusion (Hospital)	-	-	60
Field FMC to reperfusion (PHN)	-	-	90

1.6 Study context

Health funding in Australia is administered by several levels of government, with the states and territories primarily responsible for the distribution of funds to public health services (Australian Bureau of Statisitics., 2012). Consequently, each state and territory have different infrastructure design and delivery of cardiac services, driven primarily by

resources and geographical distances. This PhD thesis will focus on the Australian state of Victoria.

In Victoria, primary PCI is the reperfusion strategy for STEMI management in metropolitan hospitals and a number of regional hospitals, with intravenous fibrinolytic therapy used in regional and remote areas that do not have access to primary PCI. Most metropolitan hospitals have rapid facilitation of services for STEMI patients, with the reporting of 'DTBT' mandated by the Victorian Cardiac Outcomes Registry (VCOR) as a key performance indicator of quality of care. In 2007, a pre-hospital notification (PHN) system for STEMI care was initially trialled then implemented under the auspices of Ambulance Victoria (Hutchison et al., 2009). This particular process gave highly trained paramedics in the pre-hospital setting the capacity to acquire and transmit 12-lead ECG on a suspected STEMI patient and urgently activate the cardiac catheterisation laboratory (CCL) services.

Systems of care to support timely management of STEMI also extend into the regional and rural areas of Victoria. A pre-hospital fibrinolysis or thrombolysis program has recently been implemented across several regions, supported by an adjunctive system that provides confirmation of the 12-lead ECG STEMI diagnosis via an on-call cardiologist. Furthermore, since 2005 remote area nurses (RANs) have been utilised as co-responders to medical or trauma emergencies to improve access to medical services (Ambulance Victoria., 2018).

1.7 Thesis rationale

The rationale for this thesis is threefold. First, it is unclear whether the recently updated ESC performance targets are achievable when compared to the existing CSANZ performance targets in the setting of Australia. A comparison of achieving these divergent performance targets has not been reported in the literature, nor has the impact of the intended performance targets on health outcomes been established.

Second, there is little research pinpointing where time delay occurs, not only in the hospital systems, but over the total ischaemic time parameter. The literature reports that streamlined processes of care and communication between hospital systems and paramedic services achieve and maintain performance targets (Peterson et al., 2009). Having a deeper understanding of the factors related to time delay would enhance these systems of care. A study by Atzema et al., (2011) reported an analysis of the relationship between 'Door to ECG' time and 'ECG to Needle' time for thrombolysis management of

STEMI and calculated that a 'Door-ECG' time of four minutes was associated with the highest probability of achieving the performance target of 30 minutes (Atzema, Austin, Tu, & Schull, 2011). To my knowledge this methodology has not been applied to the reperfusion strategy of primary PCI, nor in the contemporary era of PHN systems of STEMI care. Given the prevailing but limited evidence frequently cited in STEMI guidelines suggesting a target 'Door-ECG' time ≤10 minutes (Diercks et al., 2006), it would be useful to analyse a dataset that includes not only this time parameter but other components of care, in particular 'FMC-CCL' time and 'Symptom onset-FMC' time.

Third, the time critical nature of STEMI management relies on prompt diagnosis and coordinated systems of care across various health agencies to revascularize the culprit vessel and minimise delay. Frontline clinicians, such as paramedics and emergency nurses, are pivotal to this process as primary providers of the first transaction of care to the suspected STEMI patient. To date there is little analysis of the barriers experienced by these frontline clinicians in the management of STEMI. Several studies have surveyed frontline clinicians but have focused on compliance with guidelines, prehospital thrombolysis, or more broadly the safety of emergency department systems (Kayipmaz, Ciftci, Kavalci, Karacaglar, & Muderrisoglu, 2016; Magid et al., 2009; Rajabali, Tsuyuki, Sookram, Simpson, & Welsh, 2009).

1.8 Research aims

The aim of this thesis is to explore and describe STEMI management in relation to the recommended time parameters and the barriers and enablers to achieving timely treatment, using three separate studies.

There are three research aims:

Research aim 1: To explore whether updated ESC target time parameters for STEMI management are achievable and influence health outcomes in a local setting (Study I).

Research aim 2: To measure the optimal time associated with the highest probability of achieving target time parameters for three separate parameters of care along the STEMI management continuum (Study II with three parts).

Research aim 3: To explore the perceived barriers to effective STEMI management as reported by frontline clinicians (Study III).

1.9 Specific research questions

This thesis was guided by the following research questions using three separate studies.

1.9.1 Study I research questions

a. What proportion of STEMI patients currently meet the updated ESC target time parameters?

b. When discrete groups are formed, what are the differences in clinical characteristics and health outcomes between patients meeting ESC target time parameters versus patients meeting CSANZ target time parameters?

c. What are the predictors of meeting ESC target time parameters?

1.9.2 Study II research questions (three-part study)

Before outlining the specific research questions for each part of Study II, it is important to note that two discrete subsets were formed and examined in order for analyses to be undertaken:

1) 'Hospital presenters', defined as any patient who self-presented to hospital or arrived via regular ambulance (with no pre-hospital notification (PHN)); and
2) 'PHN presenters', defined as any patient who had a confirmed STEMI diagnosis and activation of cardiac catheterisation laboratory (CCL) services prior to hospital arrival.

Research questions for Part One of Study II:

a. What is the relationship between 'FMC-ECG' time and 'ECG-reperfusion' time for both subsets?

b. What is the shortest 'FMC-ECG' time associated with the highest probability of achieving the 90-minute performance target for each subset?

c. What is the independent effect of 'FMC-ECG' time and other explanatory variables on 'ECG-reperfusion' time for both subsets?

Research questions for Part Two of Study II:

a. What is the relationship between 'FMC-CCL arrival' time and 'CCL-reperfusion' time for both subsets?

b. What is the shortest 'FMC-CCL arrival' time associated with the highest probability of achieving the 90-minute performance target for each subset?

c. What is the independent effect of 'FMC-CCL arrival' time and other explanatory variables on 'CCL arrival-reperfusion' time for both subsets?

Research questions for Part Three of Study II:

a. What is the relationship between 'Symptom onset-FMC' time and 'FMC-reperfusion' time for both subsets?

b. What is the shortest 'Symptom onset-FMC' time associated with the highest probability of achieving the 210-minute performance target for each subset?

c. What is the independent effect of 'Symptom onset-FMC' time and other explanatory variables on 'FMC-reperfusion' time for both subsets?

1.9.3 Study III research questions:

a. What are the most commonly occurring barriers to timely STEMI management for paramedics and emergency nurses?

b. Are there differences in barriers experienced by paramedics and emergency nurses?

c. Are there differences in barriers experienced by frontline clinicians in rural and metropolitan settings?

Figure 1: *Outline of thesis.*

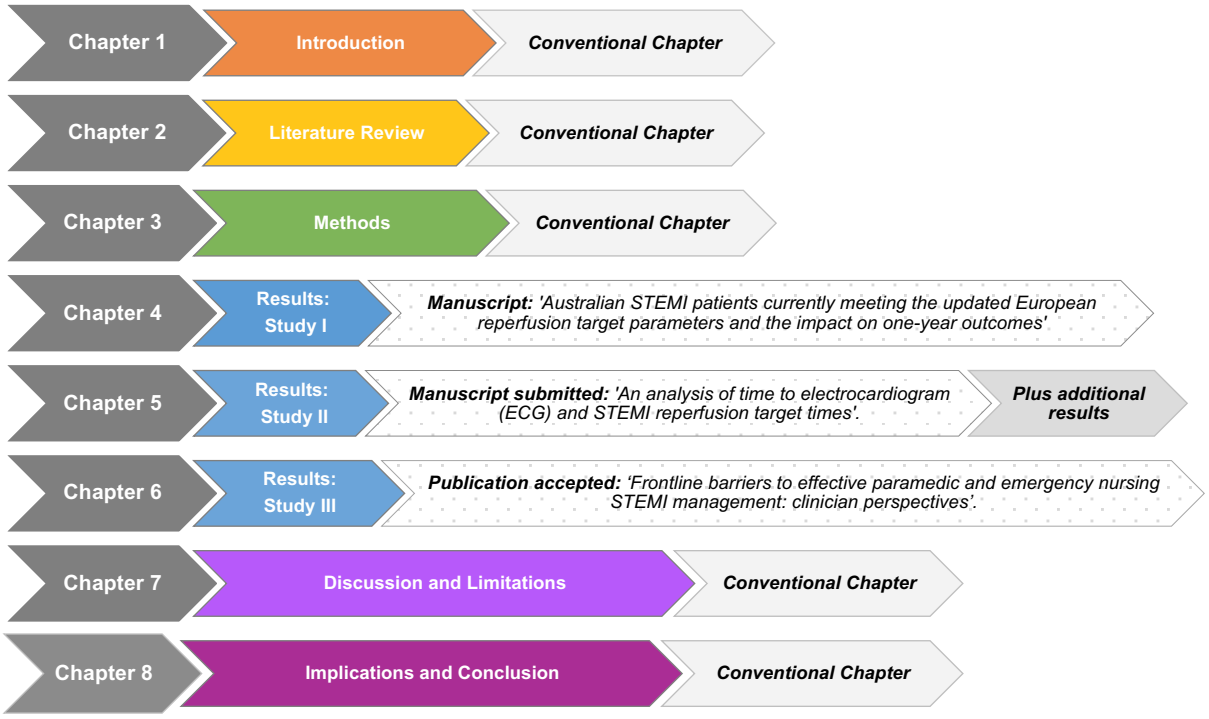

Table 2: *Overview of manuscripts/publication and alignment with research aims.*

Thesis aim	The aim of this thesis is to explore and describe STEMI management in relation to the recommended time parameters and the barriers and enablers to achieving timely treatment, using three separate studies.		
	Manuscript one	**Manuscript two**	**Publication**
Aims of paper	To establish whether updated ESC target time parameters for STEMI management are achievable and influence health outcomes in the local setting.	To calculate the optimal 'FMC-ECG' time associated with the highest probability of meeting performance parameters. **(Part One analyses only).**	To explore the perceived barriers to effective STEMI management for frontline clinicians throughout Victoria.
Study design	Cohort study of prospective and consecutive STEMI patients at a single tertiary level hospital in Melbourne.	Cohort study of prospective and consecutive STEMI patients at a single tertiary level hospital in Melbourne.	Cross-sectional survey of paramedics and emergency nurses.
Manuscript Title	***"Australian STEMI patients currently meeting the updated European Society Cardiology (ESC) reperfusion target parameters and the impact on one-year outcomes".***	***"An analysis of time to electrocardiogram (ECG) and STEMI reperfusion target times".***	***"Frontline barriers to effective paramedic and emergency nursing STEMI management: clinician perspectives".***
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1.10 Chapter summary

This chapter has outlined the structure of the thesis, defined the cardiovascular condition of interest and reported its prevalence, cost of care and rate of mortality in the Australian community. The divergent STEMI performance targets have been identified. The study context and rationale have been described, with all research aims and associated specific research questions stated.

The next chapter provides a literature review of the topics related to the central aims of the thesis.

CHAPTER 2: LITERATURE REVIEW

2.0 Chapter introduction

This chapter presents the central thesis subject, highlighting the nature of STEMI as a time critical condition over the total ischaemic time period and the need for further research to explore and better understand how to achieve timely STEMI management. The literature is reviewed to describe current understanding of STEMI pathogenesis, symptomology, diagnosis of STEMI and reperfusion strategies in STEMI, determinants of mortality risk including time to treatment, key strategies implemented to improve time to treatment in STEMI and known barriers to timely STEMI management.

The search strategies used for this literature review included an electronic search of Ovid Medline and the Cochrane Library using the following MeSH terms: Myocardial Infarction, Acute Coronary Syndrome, Angina Pectoris, Emergency Medical Services, Time Factors, Cardiology Service, Hospital, Patient Care Team, Patient Transfer, Delayed Diagnosis, Diagnostic Errors, Ambulances, Clinical Audit. Additional keywords and phrases using truncated and wildcard variations of these search terms were applied. The search was restricted to the years 2004-2019 to capture contemporary “state-of-the-art” literature in STEMI management. Literature considered seminal research but outside the restricted search period was included.

2.1 Pathogenesis of plaque rupture and coronary thrombus

The primary cause of STEMI is the sudden occlusion of a large epicardial artery (Brener, 2006). This is a pathogenic response to the acute disruption of existing atherosclerotic plaque which initiates the rapid and life-threatening formation of thrombus and subsequent coronary artery occlusion (Libby & Theroux, 2005). The conditions which cause stable atheroma to suddenly rupture, exposing thrombogenic material into the coronary lumen are thought to be inflammatory in nature, and not proportionally related to the prior severity of coronary stenoses (Ambrose & Fuster, 1998; Brener, 2006). Moreover, for approximately 50-60% of STEMI patients it is their first clinical manifestation of coronary artery disease (Ambrose & Fuster, 1998).

Atherosclerosis is a complex disease process that requires endothelial damage to provide the substrate for the accumulation of plaque within the arterial wall. Risk factors such as hypertension, smoking, hyperlipidaemia and diabetes are considered the major contributors to endothelial damage (Brener, 2006). Endothelial damage causes

endothelial dysfunction allowing the initial formation and accumulation of plaque within the vessel wall to progress outwardly before impeding coronary artery luminal blood flow; a process estimated to occur over a time period of three to five decades (Libby & Theroux, 2005).

Stable atherosclerotic plaque has a small lipid core and a thick fibrous cap providing a level of protection from potential rupture (Brener, 2006; Libby & Theroux, 2005). In contrast, a vulnerable unstable plaque has a large lipid core and a thin fibrous cap due to numerous infiltrative inflammatory mechanisms, destabilising the plaque leaving it susceptible to acute coronary thrombosis and vessel occlusion (Brener, 2006; Libby & Theroux, 2005). The consequence of prolonged vessel occlusion is irreversible myocardial cell injury leading to myocardial necrosis and potentially fatal arrythmias if not acted upon. This sequela of complete necrosis requires at least 2-4 hours to occur and is dependent on several factors: persistent or intermittent occlusion; presence of collateral circulation to the ischaemic area; pre-conditioning, and individual demand for oxygen and nutrients (Thygesen et al., 2012). All of these factors manifest for the STEMI patient as particular symptomology and diagnostic changes on the 12-lead electrocardiogram (ECG).

2.2 Symptomology of STEMI

STEMI symptomology reflects the life-threatening nature of the pathophysiology occurring. Symptoms can vary from classic or ‘typical’ in nature to diffuse or ‘atypical’ or a combination of both. Definitions of typical symptoms include chest pain/discomfort, jaw/neck pain, shoulder/arm pain, diaphoresis and dyspnoea (Shin, Martin, & Howren, 2009). In contrast, atypical symptoms include back pain, gastrointestinal distress (i.e. nausea/vomiting or epigastric symptoms), fatigue, postural nocturnal dyspnoea (PND) and palpitations/dizziness (Shin et al., 2009). Symptom incongruence can make recognition and interpretation of these symptoms difficult for both patients and clinicians (Abed, Khalil, & Moser, 2015).

The rate at which symptoms occur is considered another confounder in early recognition of STEMI, particularly for the patient (O'Donnell, McKee, Mooney, O'Brien, & Moser, 2014). O’Donnell et al., (2014) conducted a study validating two distinct ACS symptom phenomena labelled as ‘fast-onset’ or ‘slow-onset’ of symptoms, analysing the influence these had on patient-related delay. They defined ‘fast-onset ACS’ as presentation featuring chest pain (that could be accompanied by other symptoms) that was sudden,

continuous and severe in intensity. ‘Slow-onset ACS’ was defined as presentation featuring any atypical or typical myocardial infarction symptom that was gradual, intermittent (that could become continuous), and mild in intensity (but could gradually intensify) (O'Donnell et al., 2014). They concluded patients with ‘slow onset ACS’ were more likely to have longer prehospital delay. The two phenomena were considered legitimate and distinct presentations worthy of consideration when examining factors associated with delay to seeking medical treatment (O'Donnell et al., 2014).

Symptom incongruence can be explained in part by the complexity of the physiological response to myocardial ischemia and the location of visceral neural pathways in the epicardium of the heart (Meller & Gebhart, 1992). The sensory reflexes of the cardiac afferent nerves responsible for regulating heart rate, blood pressure and myocardial contractile function are also responsible for the sensation of pain during myocardial ischemia (Longhurst, Tjen, & Fu, 2001; Meller & Gebhart, 1992). It is believed two separate cardiac afferent pathways are activated during myocardial ischemia and reperfusion. The first is the sympathetic afferent pathways located in the heart that enter the upper thoracic spinal cord and, when innervated, contribute to the anginal pain experienced in the chest and arms. The second is the vagal afferent pathway which enters the cervical spinal cord, contributing to the pain sensed in the neck and jaw (Foreman, 1999; Longhurst et al., 2001; Meller & Gebhart, 1992). The innervation of these cardiac afferent pathways is related to the location and extent of myocardial ischemia, giving rise to the diverse range of symptoms patients experience (Foreman, 1999).

Another explanation for symptom incongruence in STEMI is the autonomic nervous system. It is widely reported that the structure and function of the cardiovascular autonomic nervous system in women is different to men and can explain differing clinical presentations (Dart, Du, & Kingwell, 2002). Men are more likely to have sympathetic mediated responses, such as chest pain, while females are more likely to have parasympathetic mediated responses, such as nausea and dizziness (Arslanian-Engoren & Engoren, 2010; Dart et al., 2002).

2.3 Diagnosis of STEMI

The 12-lead electrocardiogram (ECG) is the primary diagnostic tool utilised in determining the presence, location and extent of myocardial damage in STEMI. The ECG represents the electrical currents of the myocardium that dynamically change as the heart contracts and relaxes. The twelve leads of the ECG are derived from six precordial (or chest)

electrodes, three limb electrodes and a single ground electrode that represent the electrical conduction in the frontal and horizontal planes of the heart respectively (Ripa, 2012).

When a coronary vessel is deprived of blood flow, a change to the electrical activation or flow of current across the boundary of ischaemic and non-ischaemic myocardium produces a detectable injury current on the 12-lead ECG (Wagner et al., 2009). These changes include peaking of the T waves (or hyperacute T-waves), ST-segment elevation and changes in the QRS complex (Wagner et al., 2009). The 12-lead ECG changes that determine eligibility for acute reperfusion therapy are universally defined as new ST-segment elevation at the J point in two contiguous leads of 2 mm in the chest leads V2-V3, and/or 1mm in other contiguous chest or limb leads (Thygesen et al., 2018). These criteria alter slightly with age and gender and are diagnostic in the absence of left ventricular hypertrophy (Thygesen et al., 2018). A new left bundle branch block (LBBB) is considered a STEMI equivalent, representing a conduction abnormality of ventricular activation, while a pre-existing LBBB in the setting of ischemic pain requires further evaluation using Sgarbossa's criteria (Sgarbossa et al., 1996; Thygesen et al., 2018).

2.4 Reperfusion strategies in STEMI

Following diagnosis of STEMI, the fundamental treatment goal is to achieve early, complete and sustained reperfusion of the culprit epicardial artery to reduce myocardial damage to improve health outcomes. Reperfusion strategies include intravenous administration of thrombolytic agents to dissolve the clot, primary percutaneous coronary intervention (PCI) to revascularise the vessel with a coronary stent or a combination of both.

The choice of reperfusion strategy takes into consideration a patient's bleeding risk, time from symptom onset, and access to PCI-capable facilities. Two seminal studies in the early 2000's established primary PCI as superior to thrombolysis (Boersma, 2006; Keeley, Boura, & Grines, 2003). Boersma et al., (2006) demonstrated in a pooled analysis comparing 25 randomised control trials that there was a 37% risk reduction in 30-day mortality for patients receiving primary PCI compared to thrombolysis [aOR 0.63 95%CI (0.42-0.84); $p<0.001$]. Keeley et al., (2003) in a direct comparison between 23 randomised control trials confirmed an absolute risk reduction of 2% in 30-day mortality for primary PCI compared to thrombolysis (7% vs 9%; $p<0.001$) and a 5% risk reduction in combined major adverse cardiac event rates (8% vs 14%; $p<0.001$) respectively.

There is however an equipoise between one to three hours where the advantage of primary PCI loses its advantage over thrombolysis depending on factors such as time from symptom onset, infarct location and comorbid condition (Nielsen et al., 2011; Tarantini, Van de Werf, Bilato, & Gersh, 2011). Another valid and safe alternative reperfusion strategy is to administer thrombolysis prior to hospital, which has been shown to improve outcomes compared to in-hospital thrombolysis administration (Morrison, Verbeek, McDonald, Sawadsky, & Cook, 2000). In addition, a more recent strategy is to administer pre-hospital thrombolysis and immediately transfer to a PCI-capable facility integrating the two strategies (Bonnefoy et al., 2009). This strategy was validated in the CAPTIM trial measuring outcome data to five years, which found similar mortality rates compared to a primary PCI exclusive strategy, giving credence to combining the two reperfusion strategies (Bonnefoy et al., 2009).

2.5 Determinants of mortality in STEMI.

The efficacy of any of the coronary reperfusion strategies is dependent on several factors that both individually and cumulatively determine risk of mortality following STEMI. First and foremost, time to treatment is a major determinant, followed by baseline comorbid condition including advancing age, gender and cardiovascular risk. These factors will be explored in more detail below, particularly as they pertain to the reperfusion strategy of primary PCI.

2.5.1 Time to treatment

There is an immense body of evidence accumulated over several decades that demonstrates the direct relationship between the time an epicardial vessel is occluded and the extent of myocardial necrosis causing mortality. The data that relates to the reperfusion strategy of primary PCI is extensive (De Luca, Suryapranata, Ottervanger, & Antman, 2004; McNamara et al., 2006; Rathore et al., 2009; Terkelsen et al., 2010). The early work of De Luca et al., (2004) demonstrated in a cohort of 1791 consecutive STEMI patients the risk of 12-month mortality increased by 7.5% for every 30 minutes of delay to treatment. McNamara et al., (2006) supported these findings in a large analysis of 29222 STEMI registry patients by determining 6.3 fewer in-hospital deaths per 10000 treated for every 15-minute reduction in door to balloon time from 150 minutes to less than 90 minutes. Rathore et al., (2009) also concurred with the above findings in a large cohort of 43,801 STEMI patients, by expanding the time parameters to demonstrate a decrease in hospital mortality of 0.8% with a door to balloon time from 90 minutes to 60 minutes, and a further decrease in hospital mortality of 0.5% with a reduction of door to balloon time

from 60 minutes to 30 minutes. Out of the three aforementioned studies, only De Luca et al., (2004) analysed long-term mortality.

A fourth study by Terkelsen et al., (2010) was the first at the time to include the increasing use of pre-hospital notification (PHN) systems utilising emergency medical services (EMS) and examine the influence on 12-month mortality. Terkelsen and colleagues analysed 6000 patients from three high volume PCI-capable centres and found that hospital system delay was independently associated with a 10% increase in 12-month mortality per one hour of delay, and PHN system delay independently associated with an 11% increase in 12-month mortality per one hour of delay (Terkelsen et al., 2010).

Despite the previously outlined evidence of the direct link between time to treatment and mortality, there is literature reporting the lack of association between shorter reperfusion times and mortality rates, particularly as systems of care have become more sophisticated and efficient (Menees et al., 2013). Menees et al., (2013) analysed 96738 patients undergoing PCI for STEMI, and found that over a four-year period, time to treatment improved but in-hospital mortality (adjusted for age >75 years, anterior STEMI and cardiogenic shock) remained virtually unchanged (Menees et al., 2013). In contrast, Nallamothu et al., (2015) refuted Menees and colleagues' viewpoint in a larger retrospective study and using the same registry data over a longer period of time. Nallamothu et al., (2015) argued this lack of association was at an individual patient level and reflected the changing patient population receiving primary PCI; i.e. patients are older and have higher comorbid risk, as techniques and processes have evolved (Nallamothu et al., 2015).

The importance of the time taken for a patient to seek medical assistance from symptom onset or 'total ischaemic time' is highlighted in the literature as a stronger determinant of mortality and often overlooked as parameter of care. In a small study of 208 consecutive STEMI patients, Eitel et al., (2010) found a statistically significant correlation between myocardial salvage and three other factors: total time to reperfusion, ST-segment resolution, and grade of flow down the culprit vessel before reperfusion (Eitel et al., 2010). Additionally, a review article by Denktas at el., (2011) exploring the parameters of total ischaemic time acknowledges that measuring the sub intervals of care, such as door to balloon time, does not represent the substantial duration of ischemia that exists prior to hospital arrival (Denktas, Anderson, McCarthy, & Smalling, 2011).

2.5.2 Comorbid condition

Given the potentially life-threatening nature of myocardial infarction, it is not surprising the pre-existing comorbid condition of a STEMI patient is a considerable determinant of mortality. Factors such as age, gender, cardiac risk factors and previous cardiac history all account for the collective mortality risk. There are several risk-stratification tools that provide validated evidence of the likelihood of mortality such as the thrombolysis in myocardial infarction (TIMI) risk score and global registry of acute cardiac events (GRACE) score (Fox et al., 2014; Morrow et al., 2000).

Both the TIMI risk score and GRACE score model the composite effect certain comorbidities have on predicted 30-day and 1-year mortality, respectively. More specifically, the TIMI risk score is customised to STEMI patients in particular; accounting for age intervals, male gender, prior cardiac risk factors, haemodynamic condition, congestive heart failure, location of infarction and time from symptom onset (Morrow et al., 2000). In comparison, the GRACE score is inclusive of both non-STEMI and STEMI presentations and has a broader range of predictors such as age in years, gender, congestive heart failure, renal insufficiency, haemodynamic status, cardiac arrest prior to arrival, ST segment deviation (elevation or depression) and cardiac enzymes (Fox et al., 2014).

Advancing age is an established determinant of mortality in STEMI. Large scale analyses of global ACS registry data, demonstrate age to be an independent predictor of in-hospital mortality, increasing the risk by 70% for each 10-year increase in age (Granger et al., 2003). However, even though these risks exist, STEMI patients of advanced age (≥85 years of age) who are treated with primary PCI have better outcomes than if they were medically managed (Yudi et al., 2016).

The literature reporting gender as a determinant of mortality risk in STEMI is more ambiguous. There is evidence to suggest that women have double the mortality rate as men after experiencing STEMI, however once risk adjusted for age and comorbid condition these differences disappear (Movahed, John, Hashemzadeh, Jamal, & Hashemzadeh, 2009). In a large systematic review of 21 studies to determine whether gender was an independent predictor of mortality in STEMI, van der Meer et al., (2015) found that mortality in women was higher for STEMI due to their unfavourable risk profile and longer symptom-to balloon times (van der Meer, Nathoe, van der Graaf, Doevendans, & Appelman, 2015).

In more recent and local analyses, gender appears to have an independent effect on mortality risk. Khan et al., (2018) in a large multisite analysis found women were less likely to receive primary PCI, timely reperfusion, and more likely to have major adverse cardiac events (MACE) at six months than men (aOR 2.68 95% CI, 1.7- 4.09). Importantly, they found that even after adjusting for comorbid condition using the GRACE score, mortality at six months was higher in women than men (aOR 2.17; 95% CI 1.24-3.80), but interestingly there was no difference in in-hospital mortality (Khan et al., 2018). Similarly, Stehli et al., (2019) found in another large Australian multisite registry cohort that female gender was independently associated with higher for 30-day mortality using logistic regression (OR 1.67, 95% CI 1.11-2.49, p=0.01). Conversely, in contrast, Murphy et al., (2019) found no differences between gender for long-term mortality (mean follow up 4.8 years) using cox proportional hazard modelling (HR 0.99, 95% CI 0.83 to 1.18; p = 0.92) in data from the same outcome registry (Murphy et al., 2019).

2.5.2.1 Gender interactions with comorbid condition's

When comorbid conditions such as age and diabetes are examined by gender, women appear to be more disadvantaged. On average women first experience myocardial infarction around the age of 70 years and for men the average age is 66 years (Alexander et al., 2007). The effect this has on mortality is significant. Ishihara et al., (2011) in a large prospective and consecutive cohort study of 2677 STEMI patients found mortality differences in women ≥ 75 years but not < 75 years using stepwise multivariate analysis (Ishihara et al., 2011).

Additionally, the interaction between female gender and diabetes has been found to increase the incidence of coronary events. Peters et al., (2014) found in a systematic review and meta-analysis comparing diabetes risk and gender, that diabetic women were almost three times more likely to have a coronary event and diabetic men were twice as likely compared to non-diabetics (Peters, Huxley, & Woodward, 2014). Furthermore, studies have demonstrated that this interaction with diabetes is more fatal in women than men. Huxley et al., (2006) in an earlier large meta-analysis concluded diabetic women had a pooled estimated relative risk of 46% for fatal coronary events compared to diabetic men (Huxley, Barzi, & Woodward, 2006).

2.6 Barriers to timely STEMI management

Total ischemic time encompasses the entire period an epicardial vessel is occluded or at least compromised i.e. from symptom onset to reperfusion of the culprit vessel. There is extensive literature examining the influence 'patient' and 'non-patient' factors have on the delivery of timely STEMI management. The following section will explore patient-related delay and system-related delay to STEMI management, including the evident intersection of factors frontline clinicians need to rapidly navigate and respond to as the first point of contact to the presumed STEMI patient.

2.6.1 Patient-related delay

Patient-related delay has been studied extensively over several decades as an area with potential for improvement, but little has changed. Despite major effort put into public health campaigns and studies to understand factors that underpin health seeking behaviour, patient decision delay remains the largest component of delay for total ischemic time. An extensive retrospective study reported that patient-related delay had remained largely unchanged over 20 years, with both men and women >75 years of age more likely to delay seeking treatment (Nguyen et al., 2010).

Two formative randomised control trials designed to address patient related delay investigated the impact an educational intervention had on the health seeking behaviour of patients who had existing coronary artery disease (Dracup et al., 2009; Mooney et al., 2014). Both studies randomised samples into an experimental group that received education and counselling about symptomology and actions required and compared them with a control group. The investigators of both studies carried out power analysis to calculate sample size and demonstrated adequate power to detect differences in pre-hospital delay time between groups. In a sample of 3522 participants, Dracup et al., (2009) concluded the intervention had no impact on pre-hospital delay for those patients who were readmitted with an ACS, nor an increase in the use of emergency medical services (EMS) / ambulance services (Dracup et al., 2009). In contrast, in a sample of 1944 participants, Mooney et al., (2014) demonstrated a statistically significant lower pre-hospital time of six-hours for the experimental group, but again found no difference between groups for ambulance use (Mooney et al., 2014).

There is a plethora of literature that shows strong associations between specific factors and patient-related delay. These being older age, self-transportation to hospital diabetes, existing cardiac risk factors, lower income, social support, gradual/intermittent symptoms, fearing the consequences of seeking help and attributing the symptoms as non-cardiac

(Dracup et al., 1995; Kirchberger, Heier, Wende, von Scheidt, & Meisinger, 2012; McKee et al., 2013; McKinley et al., 2011; O'Brien, O'Donnell, McKee, Mooney, & Moser, 2013; Thylen et al., 2015).

The relationship between patient-related delay and subsequent treatment has also been examined, with time to presentation not only an independent predictor of prolonged time to reperfusion, but also associated with the reduced likelihood of receiving any primary reperfusion therapy (Ting, Bradley, et al., 2008). Additionally, there is evidence that 12-month health outcomes are impacted. This was demonstrated in a recent prospective Australasian study on patients presenting with a possible ACS (Cullen et al., 2016). A presentation time of more than 6 hours from symptom onset for those diagnosed with ACS was associated with a 57% increase in the rate of the composite primary endpoint (death; myocardial infarction; unstable angina requiring revascularisation; or readmission with heart failure) compared to a presentation time of 6 hours or less from symptom onset (Cullen et al., 2016).

2.6.2 System-related delay

There are several known system-related factors that potentially prolong the delivery of timely STEMI management; namely time of presentation, overcrowding in emergency departments, and under-triaging or mis-dispatch of emergency services. The initial interaction frontline clinicians have with the presumed STEMI patient may also play a role in timely management and will be further explored in the following sections.

2.6.2.1 Time of patient presentation

For most PCI-capable health services, only 40 hours (or 24%) of the available 168 hours of any given week are considered ‘operational’ or ‘business’ time. The time a patient presents to health services can determine the time taken to deliver STEMI management due to the limited availability of operational resources.

Magid et al., (2005) was one of the first to demonstrate a relationship between time of presentation and prolonged time to STEMI management. Comparing over 100 000 STEMI patients in a multisite registry, they found statistically significant longer door to balloon times of 21 minutes for patients, and a higher adjusted rate of in-hospital mortality at 7% (Magid et al., 2005). These findings have been replicated in several subsequent studies examining the relationship between presentation time and time to treatment, with varying differences found regarding the impact on mortality (Redfors et al., 2017; Tscharre et al., 2017; Wang et al., 2017).

Both Redfors et al., (2017) and Tcharre et al., (2017) in analyses of large multisite registries confirmed the impact of presenting out of hours on time to treatment but found no differences in either short or long-term mortality (Redfors et al., 2017; Tscharre et al., 2017). In contrast, Wang et al., (2017) in a meta-analysis of 30 studies concluded presenting out of hours increased short-term mortality by 7% but not long-term mortality with a median follow up of 2.5 years (Wang et al., 2017).

2.6.2.2 Overcrowding

There are many studies in the literature reporting the impact overcrowding in the Emergency Department (ED) has on timely STEMI management, which in some studies extends to an impact on health outcomes. Jones et al., (2014) demonstrated in an analysis of 272 hospitals, ED overcrowding was associated with poorer PCI performance. In their study, this finding was consistent across all measures of crowding and efficiency, and these relationships remained statistically significant when adjusted for acuity data (Jones, Sonnad, Augustine, & Reese, 2014). Pines et al., (2009) in a retrospective study of 4574 patients found an association between longer waiting room times and the rate of adverse outcomes in acute coronary syndrome (ACS) compared to non-ACS patients (OR 3.7, 95% CI 1.3-11) (Pines et al., 2009). Kulstad et al., (2009) in a study using a validated score to measure the degree of overcrowding (EDWIN score), found patients with higher EDWIN scores were more likely to have prolonged time to treatment in STEMI (Kulstad & Kelley, 2009). Schull et al., (2004), in a large study of 3452 STEMI patients and using multivariate analysis found that moderate to high crowding conditions in the ED were independently associated with prolonged time to treatment for both reperfusion strategies of thrombolysis and primary PCI (Schull, Vermeulen, Slaughter, Morrison, & Daly, 2004).

Hospital ED overcrowding also impacts paramedic services. Ambulance diversion for greater than 12 hours was associated with a higher 30-day mortality compared to no diversion status in a large case study of over 13000 patients with STEMI (Shen & Hsia, 2011). Emergency response times (ERT) of time critical emergencies for paramedics were analysed in a local study, finding an independent association of ERT when there was hospital delay time from the previous hour (Nehme, Andrew, & Smith, 2016).

Some doubts about the impact ED overcrowding has on time to treatment in STEMI are raised in the literature. Bernstein et al., (2009) in a review article of 43 papers concluded there was growing evidence that overcrowding in ED is associated with reduced timelines of care and mortality, particularly for patients with pneumonia, but reported the association

was not strong enough to determine this disparity of care extended to STEMI management (Bernstein et al., 2009). Despite some ambiguity, overall, the literature suggests that over-crowding may be a factor that affects timely STEMI management.

2.6.2.3 Under-triaging / mis-dispatch of STEMI patients

From the start of the first transaction of care, patient triage at hospital or dispatch of the paramedic services has potential to delay STEMI management. Misclassification of triage scores or under-triaging of potential STEMI patient is widely reported (Atzema, Austin, Tu, & Schull, 2009; Kuhn, Worrall-Carter, Ward, & Page, 2013; Ryan et al., 2016). Atzema et al., (2009) found in a retrospective analysis of 3088 patients presenting with symptoms suggestive of myocardial infarction 44% of confirmed STEMI diagnoses were under-triaged, and this was independently associated with delay to STEMI reperfusion strategies. Similarly, Ryan et al., (2016) reported a 20% lower urgency triage score for STEMI patients than the recommended international guidelines. Attenuating factors such as absence of chest pain, older age and female gender were found to define characteristics of the under-triaged group (Ryan et al., 2016). In a large multisite Australian study of 21080 acute myocardial infarction patients by Kuhn et al., (2013), under-triaging of patients was found to be the factor most strongly associated with delayed treatment. This study analysed patients presenting across Victorian ED's, and used regression tree analysis to understand factors that influenced timely management (Kuhn et al., 2013).

Correspondingly, the paramedic service also relies on an initial phone-based triage of reported symptoms from the care seeker to dispatch ambulance services. Inappropriate dispatch to a field scene based on telephone triage has potential to delay time to treatment (Coventry, Bremner, Jacobs, & Finn, 2013; Fourny et al., 2011; Lindstrom, Heikkila, Bohm, Castren, & Falk, 2014). Fourny et al., (2011) found in a prospectively collected registry that 30% of STEMI patients had an initial inappropriate dispatch of paramedic services. This also impacted upon the time to reperfusion (Fourny et al., 2011), and was a similar finding to the above mentioned studies examining under-triaging in hospitals. In a qualitative study by Lindstrom et al., (2014) they deduced barriers to the assessment decision making around dispatch were 'contradictory information from the care seeker', 'absence of the primary problem/symptom reported by the care seeker ' and 'structure of the emergency call' (Lindstrom et al., 2014). In a large analysis of gender differences in the dispatch of paramedic services for STEMI by Coventry et al., (2013), using multivariate analysis they found that women with chest pain were 61% less likely to be allocated the

highest priority of dispatch (lights and sirens) than men with chest pain; OR 0.39, 95% CI 0.18 -0.87; p=0.02 (Coventry et al., 2013).

2.6.3 Challenges for frontline clinicians

Paramedics and emergency nurses are often the first point of contact with the health system for the presumed STEMI patient, playing a pivotal role in the subsequent trajectory of care. The clinical judgement required to diagnose STEMI is time sensitive and requires expertise to rapidly collect a brief but accurate clinical history and elicit symptom characteristics. The potential barriers for this decision-making process are multifactorial and include the environmental context within which they occur. These barriers will be discussed in the following sections.

The ability to make rapid clinical decisions is a fundamental skillset essential to frontline clinicians in diagnosing STEMI. Bucknall (2003), in a qualitative study of the influences nurses experienced in clinical decision making, found familiarity with particular patient conditions, the availability of resources/technology, and supportive and collaborative interpersonal relationships were the main enablers in reducing the burden of rapid decision making in critical care environments (Bucknall, 2003). In a more recent literature review of paramedic judgement and decision-making skills by Perona et al., (2019), it was established paramedics displayed a high level of reasoning and aptitude in rapidly gathering patient cues and problem solving with minimal information. The ability to collect, process and utilise this information was, naturally, more developed for experienced paramedics compared to novices (Perona, Rahman, & O'Meara, 2019).

Variation and incongruence of STEMI symptomology has been explored in the above section of this chapter and is reported in the literature as a barrier at the individual frontline clinician level to the delivering of timely STEMI management or misdiagnosing it entirely. This is particularly the case when the patient's symptoms are atypical in nature or there is an absence of chest pain altogether (Park et al., 2014; Pope et al., 2000). Using data from a large propensity matched cohort of STEMI patients, Park et al., (2014) analysed the impact on outcomes for patients presenting with non-chest pain symptoms. They found presenting with no-chest pain was independently associated with delayed diagnosis and reperfusion but not mortality (Park et al., 2014). In another, albeit older but still relevant, multisite study of 10689 patients presenting to hospital with symptoms suggestive of cardiac ischemia, Pope et al., (2000) found 2.1% of the 899 patients with acute myocardial infarction were mistakenly discharged home. In multivariate analysis

those patients not hospitalised with a missed diagnosis were 1.9 times more likely to have 30-day mortality when risk adjusted. Furthermore, patients whose primary presenting symptom was shortness of breath were 2.7 times more likely not to be hospitalised (95% CI 1.1-6.5), and if female and < 55 years of age were 6.7 times more likely not to be hospitalised (Pope et al., 2000).

Interpretation of 12-lead ECG changes can also add to the complexity of decision making required. To reliably differentiate between a new or old bundle branch block pattern can be difficult for frontline clinicians when they have limited access to previous patient history (Bansilal et al., 2011). ST-segment elevation can also be indicative of other pathologies, such as pulmonary embolus, intracranial processes, myocarditis, pericarditis, stress cardiomyopathy (Takotsubo), early repolarization, various channelopathies, and electrolyte abnormalities (Thygesen et al., 2018). There is an array of automated proprietary diagnostic algorithms used to assist with ECG decision making particularly for paramedics, which have been shown to have varied specificity and sensitivity in diagnosing STEMI (Clark, Sejersten, Clemmensen, & Macfarlane, 2010; Garvey, Zegre-Hemsey, Gregg, & Studnek, 2016).

The literature also identifies the environmental context frontline clinicians operate in as a factor that potentially impacts the ability to deliver effective STEMI management; such as technical challenges related to the acquisition and transmission of the pre-hospital ECG, along with predictors of ambulance response times (Al-Zaiti, Shusterman, & Carey, 2013; Do, Foo, Ng, & Ong, 2013; Nehme et al., 2016). Al-Zaiti et al., (2013) in a review article identifies seven major technical challenges in the transmission of the prehospital ECG, such as inconvenience and transport delay for the paramedics, interpretation errors, signal noise, equipment malfunction, transmission failure, reliability of mobile phone networks (Al-Zaiti et al., 2013). Furthermore, predictors of prolonged ambulance response times have been explored. Do et al., (2013), in a large retrospective study of electronically collected dispatch data, found the volume of calls in the previous hour prolonged ambulance response times (ART), however patient factors had little effect on ART (Do et al., 2013). Similarly a study by Nehme et al., (2016) found response times were independently associated with distance to scene, case upgrade, hour and day to the week, workload in the previous hour, ambulance skill set, and average hospital delay time (Nehme et al., 2016).

2.7 Key strategies and factors that improve time to treatment in STEMI

For almost two decades the integration of the evidence-based ACS guidelines into local practice has driven the development and evaluation of processes of care that deliver timely STEMI treatment. The following section will review the literature that explores the strategies and factors found to improve the delivery of effective STEMI management at an organisational and clinical level.

2.7.1 Organisational culture

A positive organisational culture is a fundamental contributor to sustained quality improvement. According to Taylor et al., (2015) five cultural characteristics are present in a positive organisational culture: 'trust and respect', 'unwavering quest for excellence', 'recognition and compensation for good work', 'safe, non-threatening environment' and 'an organisational wide vision or mission' (Taylor, Clay-Williams, Hogden, Braithwaite, & Groene, 2015).

There is evidence of this wide vision in the STEMI literature with separate position statements by the National Heart Foundation of Australia (NHFA) and the American Heart Association (AHA) that call for the adoption of a universal approach to STEMI management and cardiovascular care at an organisational level (Maddox et al., 2017; National Heart Foundation of Australia., 2012). Both bodies appeal for systems of care to be fostered, activated and supported on a national scale. In particular, the NHFA calls for clinical leadership to be collaborative across service delivery boundaries with early diagnosis of STEMI, prioritisation of catheterisation laboratory services, appropriately trained workforce, and performance monitoring and feedback mechanisms informing systems of care (National Heart Foundation of Australia., 2012). Furthermore, the AHA identifies four domains to focus on: science and informatics, patient-clinician partnerships, incentives, and development of a continuous learning culture (Maddox et al., 2017).

The aforementioned suggestions for organisational cooperation have been addressed in a recent mixed-methods longitudinal study termed Leadership Saves Lives (LSL). This study analysed the influence organisational culture had on clinical outcomes in myocardial infarction across ten hospitals (Curry et al., 2018). They established five pre-defined culture domains influenced clinical outcomes, these being: (1) learning environment, (2) senior management support, (3) psychological safety, (4) commitment to the organisation and (5) time for improvement. Curry et al., (2018) found six of the ten hospitals had significant changes in three of the culture domains; learning environment, senior management support and psychological safety (i.e. shared belief in speaking out without

punishment), along with a reduction in risk-standardised mortality rate over a 24-month period (Curry et al., 2018).

More broadly, yet importantly, the organisational culture of the health service delivery system requires framing around the diffusion and dissemination of innovations. Determinants of attaining and maintaining this state require an understanding of system antecedents, system readiness, adoption/assimilation, communication, process of implementation and how together they operate within the wider environment of the organisation (Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004). When these core concepts of organisational culture operate in concert, strategies that promote efficient and effective clinical processes of care have the potential to thrive.

2.7.2 Hospital processes of care

At a clinical level, robust hospital processes of care are paramount to the delivery of timely STEMI management. There are many examples in the literature reporting how hospital processes have led to improved time to treatment in STEMI management (Ahmar, Quarin, Ajani, Kennedy, & Grigg, 2008; Krumholz et al., 2011; Willson et al., 2010). However, the extensive work undertaken by Bradley et al., in two particular studies identified and quantified system-based determinants that improve access to timely STEMI management (Bradley, Herrin, et al., 2006). Cardiac Catheter Laboratory activation systems of 365 United States hospitals were analysed with six strategies significantly associated with reduced door to balloon times: 1) the activation of the catheterisation laboratory by emergency physicians, 2) having a single call page to activate the catheterisation laboratory; 3) having pre-hospital activation of catheterisation services; 4) expecting staff to be 20 minutes away instead of 30 minutes away from the hospital; 5) having an attending cardiologist 24/7 onsite and 6) employing a real-time data feedback system as a quality assurance measure (Bradley, Herrin, et al., 2006).

In addition to this, Bradley et al., (2006) qualitatively explored timely STEMI management in another study using in-depth interviews to examine the successful approaches hospitals used to achieve STEMI guideline targets (Bradley, Curry, et al., 2006). They found eight themes that characterised success: 1) commitment to an explicit goal to improve DTBT motivated by internal and external pressures; 2) senior management support; 3) innovative protocols; 4) flexibility in refining standardised protocols; 5) uncompromising individual clinical leaders; 6) collaborative teams; 7) data feedback to monitor progress and identify problems and successes. 8) and organisational culture that fostered resilience to challenges or setbacks (Bradley, Curry, et al., 2006).

The strategies examined in the previously described studies streamline and characterise efficient and effective timely STEMI management at a clinical level, and as such, have informed and influenced the STEMI guidelines, all of which espouse the importance of adopting and implementing such strategies (Chew et al., 2016; Ibanez et al., 2018; O'Gara et al., 2013).

2.7.3 Pre-hospital processes of care

The utilisation of pre-hospital notification (PHN) systems integrated into existing hospital processes of care has grown exponentially worldwide over the last decade. Pre-hospital triage of the presumed STEMI patient by emergency medical services (EMS)/ ambulance services minimises hospital-based delay and reduces time to treatment (Drew et al., 2011). Rokos et al., (2009) in a pooled analysis of ten independent prospective observational registries reported patients who presented with pre-hospital triage and diagnosis of STEMI achieved the time parameter of <90 minutes 86% of the time (Rokos et al., 2009). In a randomised controlled trial known as the SMART study, Drew et al., (2011) demonstrated a statistically significant reduction in time from emergency call to 12-lead-ECG for those patients having a prehospital ECG (Drew et al., 2011). Locally, the widely published Australian trial evaluating a PHN system named the MonAMI trial commenced in 2007 (Hutchison et al., 2009). A recent evaluation of the long term effectiveness of this particular PHN system of care for the first 1000 consecutive patients of the MonAMI trial concluded reduced time to treatment was sustained (Hutchison, Malaiapan, Cameron, & Meredith, 2013). A more recent systematic review and metanalysis of the benefits of PHN systems of care found pre-hospital diagnosis and advanced notification of STEMI patients reduced time to treatment and, importantly, was associated with reduced rates of short-term mortality (Nam, Caners, Bowen, Welsford, & O'Reilly, 2014).

Pre-hospital systems of care cross service delivery boundaries and rely on robust process to be efficient and effective. A scientific statement from the European Society of Cardiology on the pre-hospital treatment of STEMI patients emphasises the importance all clinicians have in the process of care, championing the collaborative role paramedics and nurses have in optimising pre-hospital STEMI systems to administrative and policy decision makers (Tubaro et al., 2011).

2.8 Chapter summary

A review of the literature has been presented in this chapter relevant to the research aims of this thesis. The literature confirms STEMI as a time critical condition, with evidence-based guidelines suggesting specific target performance parameters to reflect this. However, the evidence supporting a time to ECG target of less than 10 minutes is limited and presents a gap in the literature. This also presents an opportunity to examine the impact other pertinent time frames related to the total ischaemic time continuum have on achieving target performance parameters.

The recently divergent ESC STEMI guidelines distinguish between mode of presentation and are also underexamined in the literature in terms of achievability and impact on outcomes compared to other existing international STEMI guidelines. This gap in the literature also presents an opportunity to explore and compare differences.

This literature review also identified a range of factors that affect timely STEMI management and patient outcomes, including patient-related and system-related characteristics. The way in which guidelines support system improvement was explored through reviewing some of the strategies and factors that have been used to try to improve timely STEMI management. However, the critical role frontline clinicians have in what is a complex system of care is under-reported and little known about their experiences.

The next chapter will describe the methods used for the three studies undertaken and reported in this thesis.

CHAPTER 3: METHODS

3.0 Chapter introduction

This chapter is divided into three sections and will describe the individual methodologies applied to the three separate studies that form this PhD thesis. All three sections will detail the study site and population, inclusion/exclusion criteria, ethics approval, data collection for Studies I & II, survey development for Study III, and statistical analyses used for each individual study. Studies I and II examine data from the same cohort of ST segment elevation myocardial infarction (STEMI) patients, with distinct exclusion criteria applied to Study I and each part of Study II. While, Study III examines barrier's in the delivery of STEMI management as perceived by frontline clinicians' using a stakeholder survey.

3.1 Overview for study I

Study I examines the contrasting STEMI performance targets espoused by the updated European Society of Cardiology (ESC) and existing Cardiac Society of Australia and New Zealand (CSANZ) guidelines. The primary research question is to establish the proportion of STEMI patients meeting the updated ESC 'time to reperfusion' target parameters of ≤90 minutes according to mode of presentation; i.e. from 'door' or 'field' first medical contact (FMC). The second research question is to compare differences between characteristics and health outcomes for patients achieving the ESC or CSANZ target parameters, and the third research question is to identify predictors of achieving the ESC target parameters.

3.1.1 Study site and population

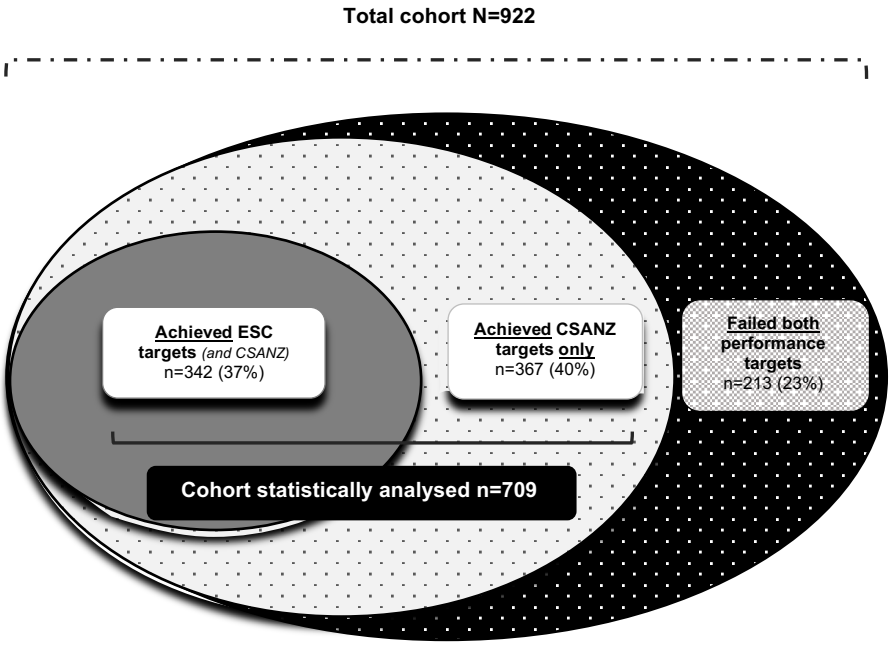
This study took place in a tertiary level university affiliated metropolitan Australian hospital. A consecutive cohort of 922 STEMI patients was evaluated. Primary percutaneous coronary intervention (primary PCI) was the exclusive reperfusion strategy for patients suspected of experiencing a STEMI at this site. The data analysed in this study was collated over a specific period of time from July 2009 to December 2017. Prior to this particular time period, in April 2008 an expedited system of care for STEMI patients called the 'Cath Lab Code' was implemented. July 2009 marked the operationalisation of a pre-hospital notification (PHN) system integrated into this existing hospital system of care for STEMI patients. Therefore, the two systems of care were operational over the period of analysis.

3.1.2 Inclusion/exclusion criteria

All patients who were admitted through the Emergency Department (ED) with STEMI and went on to have primary PCI were included (n=922). Patients not included in this cohort were urgent Non-STEMI patients; STEMI patients with normal angiography, STEMI patients who required no intervention or failed intervention; and interdepartmental STEMI patients and inter-hospital STEMI transfers. To address the first research question for Study 1 we established the proportion of target time achievement for both sets of guidelines for the total cohort of 922 STEMI patients, using existing and retrospectively applied time point data.

To address the second and third research questions of this study, further exclusion criteria were applied. The final cohort statistically analysed were the STEMI patients who achieved timely reperfusion targets (n=709). These were then separated into discrete groups; patients who achieved the CSANZ target only (n=367) or patients who achieved the ESC target (n=342). By definition patients who achieved the ESC targets had also achieved the CSANZ target but were examined as a distinct group (see Figure 2).

Figure 2: *Venn diagram illustrating formation of discrete groups (Study I).*



3.1.3 Ethics approval

This study utilised a database with existing institutional HREC approval and conformed to the relevant ethical guidelines for quality assurance projects [approval numbers H2011/04271, LNR/14/Austin/320]. In addition, La Trobe University granted research ethics approval to undertake particular time point analysis as part of the greater body of work for this thesis [approval number S17-011]. *(See appendices 3,6,7)*

3.1.4 Data Collection

The data analysed in Study I was obtained from a database maintained by the Cardiac Catheterisation Laboratory (CCL) at a tertiary level Australian hospital. Data is collected prospectively to capture STEMI management performance as part of an ongoing quality improvement program. Baseline clinical and procedural characteristics, along with specific time point data across the STEMI management continuum are recorded for all patients presenting to this hospital's ED.

The baseline clinical characteristics, mode of presentation and procedural characteristics are recorded using a chart review of the patient's medical file record performed at or near the time of admission by an experienced clinician. Demographic characteristics such as age and gender are recorded. Additional data includes time of presentation, stratified by arrival to hospital within operating business hours (Monday-Friday; 08:00hrs-18:00hrs) or out of these operating business hours. Mode of presentation is categorised as 'hospital presentation' (either self-presentation or via the regular ambulance) or 'PHN presentation'.

Cardiac risk factors and cardiac history are recorded. Clinical characteristics such as symptomology, comorbid conditions and outcomes are documented for each STEMI patient. Typical or atypical symptomology is defined as per the ten descriptions of Shin *et al.* (Shin et al., 2009). Typical: chest pain, pressure or discomfort; diaphoresis; shoulder/arm pain; jaw/neck pain; or dyspnoea. Atypical: back pain; tiredness/fatigue; gastro-intestinal (GI) distress- such as nausea, epigastric or vomiting; palpitations; dizziness/faintness; or paroxysmal nocturnal dyspnoea. Fast onset or slow onset of symptomology is defined as per O'Donnell *et al.* (O'Donnell et al., 2014). Fast onset: as the main symptom of chest pain tightness/discomfort that is sudden continuous and severe. Slow onset: as any typical or atypical symptom that is gradual or intermittent which may become continuous; or mild which may gradually become intense.

Clinical risk profile is assessed for each patient using the Thrombolysis in Myocardial Infarction (TIMI) risk score. This validated composite scoring system takes into account age, haemodynamic status, cardiac risk factors, symptom onset, location of infarct, and Killip class to predict 30-day mortality and can be considered a proxy for comorbid condition (Morrow et al., 2000).

Procedural characteristics are also recorded prospectively and include, type of arterial access i.e. trans-radial or trans-femoral, insertion of intra-aortic balloon pumps (IABP) pre reperfusion, and 'TIMI grade flow' 0-3 pre and post reperfusion i.e. TIMI 0 flow representing total occlusion of vessel, through to TIMI 3 flow representing normal perfusion (Chesebro et al., 1987).

Health outcomes are also prospectively charted including biochemical markers of myocardial injury such as peak Creatine Kinase (CK) units/litre, peak cardiac Troponin I (cTn-I) and high sensitivity Troponin T I (hsTn-T) ng/L assays. In addition, diagnostic left ventricular ejection fraction (LVEF) as assessed by transthoracic echocardiogram (TTE) up to six weeks post index admission to enable an estimate of infarct size. Length of hospital stay, and in-hospital mortality are also recorded. Mortality rates out to 12-months are obtained from two registries; the Melbourne Interventional Group (MIG) outcome registry from the year 2009-2011 and the Victorian Outcomes Registry (VCOR) from 2012-2017 , which have previously been described in the literature (Ajani et al., 2006; Stub et al., 2018).

Central to this database are six pre-specified time points of STEMI care that are prospectively documented at the time of indexed admission. This data collection uses a standardised protocol to record each time point with the data source of each time point regularly audited and synchronised to correct time and date. Table 3 provides a clear outline of the six specific time points of care and the sources they are derived from.

Table 3: *Outline of time points collected (Study I and II).*

Specific time point	Definition	Source(s)
Time 1: Symptom onset	Self-reported time of symptom onset that brought patient into hospital.	Documented from either paramedic notes or hospital record according to mode of presentation.
Time 2: Door time*	First medical contact (FMC) with hospital system	Documented from electronic record - triage time for hospital presenters. - or arrival time for PHN presenters.
Time 3: ECG time	Time of first diagnostic ECG	Documented from hospital ECG or field (pre-hospital) ECG.
Time 4: CCL activation	Time of activation of CCL services	Documented from dedicated Cath Lab pager located in department.
Time 5: CCL arrival	Time of patient arrival in CCL	Prospectively documented by Cath Lab team.
Time 6: Reperfusion time	Time of first balloon inflation or device aspiration.	Prospectively documented by Cath Lab team.

Note: * For this database time to reperfusion is calculated from 'Door time'.

To examine the primary research question for 'Study I', the additional timepoint of 'first field FMC for PHN presenters was located and documentation of time to treatment according to the ESC definition calculated. As part of the second research question distance to the treating hospital for PHN patients were also recorded to provide context to the entire field to reperfusion time. Distance was documented using scene postcode and calculating distance in kilometres to the destination hospital using the website https://www.freemaptools.com/find-australian-postcodes-inside-radius.htm

3.1.5 Statistical analyses

There were several methods utilised to address the three research questions for Study I. The first research question was addressed by reporting the descriptive statistics of the proportion of time CSANZ and ESC guidelines were achieved. The second research question was addressed by reporting categorical and continuous variables and undertaking univariate analysis to compare groups using Chi square analysis, Student's t-test or Mann-Whitney *U* test where applicable. The Kaplan-Meier method was used to estimate cumulative incidence of all-cause mortality out to 12-months between target

groups using the log rank test. The third research question was addressed by using two methods of multivariate analyses: logistic regression and cox proportional hazard ratio modelling. Variables with p values <0.10 identified (Ranganathan, Pramesh, & Aggarwal, 2017) in univariate analysis were entered into the separate models, respectively, to determine independent predictors of achieving ESC reperfusion targets and survival out to one-year. Both regression analyses adjusted for the same four variables; age, TIMI risk >5, cardiac arrest and intubation prior to Cardiac Cath Lab arrival. Statistical analysis was performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp., Armonk, N.Y., USA). Statistical significance was set at $p<0.05$.

3.2 Overview for Study II

Study II examines the effect specific time points of STEMI care have on the end point of time to reperfusion. This study has three distinct parts to reflect the time points of care examined. In addition to this, two discrete subsets were formed to analyse the separate systems of care that intersect once a patient arrives to hospital: “hospital presenters” and “PHN and presenters”.

Part One examines ‘FMC-ECG’ time and the proceeding time to reperfusion for both subsets. The first research question is to identify the relationship between ‘FMC-ECG’ time and ‘ECG-reperfusion’ time. The second research question is to calculate the shortest ‘FMC-ECG’ time associated with the highest probability of achieving the ≤90-minute target. The third research question is to calculate the independent effect covariates of interest have on ‘ECG-reperfusion’ time.

Part Two examines ‘FMC-CCL’ time and the proceeding time to reperfusion time for both subsets. The first research question is to identify the relationship between ‘FMC-CCL’ time and ‘CCL-reperfusion’ time. The second research question is to calculate the shortest ‘FMC-CCL’ time associated with the highest probability of achieving the ≤90-minute target. The third research question is to calculate the independent effect covariates of interest have on ‘CCL-reperfusion’ time.

Part Three examines ‘Symptom onset-FMC’ time and the proceeding time to reperfusion for both subsets. The first research question is to identify the relationship between ‘symptom-FMC’ time and ‘FMC-reperfusion’ time. The second research question is to calculate the shortest ‘symptom-FMC’ time associated with the highest probability of achieving the ≤210-minute target. The third research question is to calculate the independent effect covariates of interest have on ‘FMC-reperfusion’ time.

3.2.1 Study site and population

The study site and population for Study II was the same as outlined in section 3.1.1. for Study I. The data analysed in Study II was over a period time when both the internal 'Cath Lab Code' system and the PHN system of care were integrated and fully operational for all STEMI patients who presented to the ED.

3.2.2 Inclusion/exclusion criteria

To address the individual research questions for Study II, three unique cohorts were formed. Analysis was restricted according to which part of the study was examined. For Part One patients with an 'FMC-ECG' time ≥90 minutes were excluded after which point it would be impossible to achieve performance targets. Similarly, for Part Two and Three, patients with an 'FMC-CCL' time ≥ 90 minutes and a 'Symptom onset-FMC' time ≥ 210 minutes were also excluded respectively. Figures 3 and 4 illustrate the exclusion process according to which time point was examined. These conditions were similar to the exclusion criteria Atzema and colleagues applied in their study (Atzema et al., 2011).

Figure 3: *Exclusion process for final cohorts analysed (Study II all Parts).*

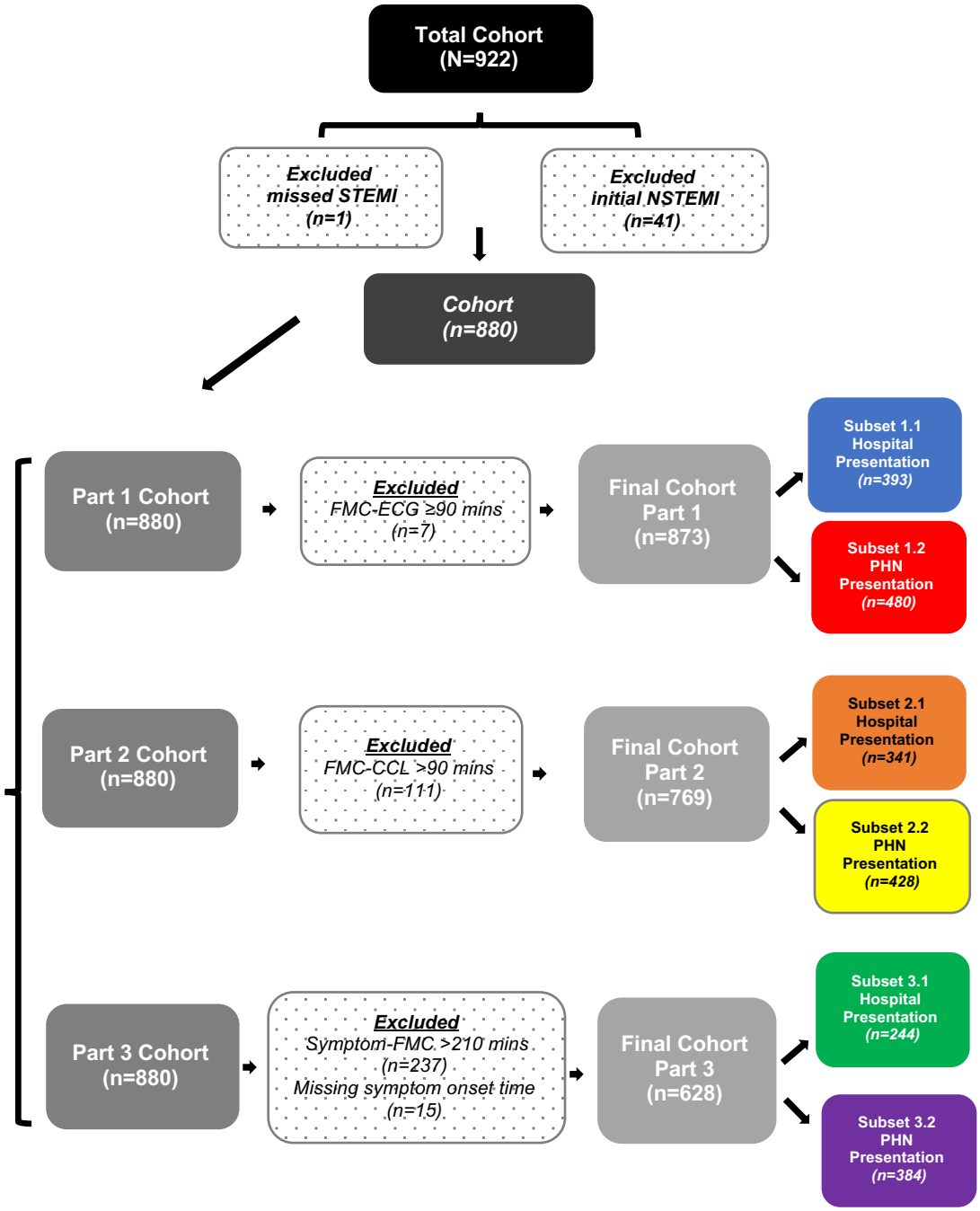
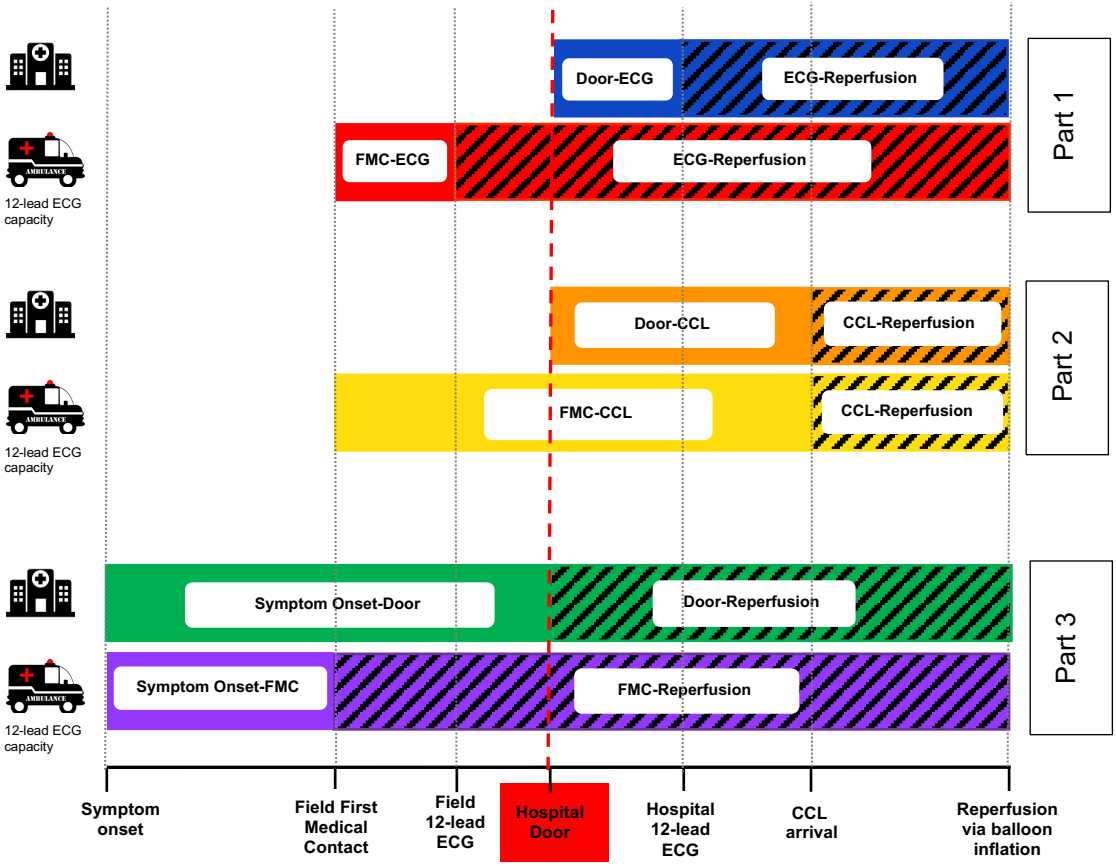


Figure 4: *Graphical display of each part of time point analysis (Study II all Parts)*



3.2.3 Data collection

The data analysed in Study II were obtained from the same database described in Study I. There were some subtle differences in the variables of interest for Study II. Identical time points of STEMI care were utilised in this study, including field 'FMC' time to account for the discrete cohorts examined as separate subsets. Patients were excluded from analysis if the first timepoint analysed exceeded the composite timepoint examined i.e. patients with FMC-ECG times greater than or equal to 90 minutes were excluded from analysis due to the fact it would be impossible for them to achieve timely reperfusion targets *(See figure 3).* The same baseline clinical, presentation and procedural characteristics were the primary variables of interest for the three parts of Study II. However, outcomes such as mortality were outside the scope of the research objectives and therefore not included in the analyses for this study.

3.2.4 Ethics approval

The ethics approval for Study II was approved under the same application as Study I. [approval numbers H2011/04271, LNR/14/Austin/320 and S17-011]. *(See appendices 3,6,7)*

3.2.5 Statistical analyses

As a first step, univariate analyses compared the baseline clinical characteristics and outcomes for the subsets 'hospital presenters' and 'PHN presenters' to provide context and explain potential variation in subsequent results. Student's t-test or Mann U Whitney test were used where appropriate for continuous variables and Chi square analysis for categorial variables. Statistical analysis was performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp., Armonk, N.Y., USA). Statistical significance was set at $p<0.05$. The statistical analyses performed for Study II were identical for Parts One, Two and Three.

The first research question was addressed by using smoothing splines to model the relationship between specific timepoints for each subset: i.e. 'FMC-ECG' and 'ECG-reperfusion' time; 'FMC-CCL' and 'CCL-reperfusion' time; and 'Symptom-FMC' and FMC-reperfusion' time. Smoothing splines fit nonparametric data by joining two or more polynomial curves, with the location of these joins known as knots (Wood, 2006). This curve fitting process tested eight models, using both basic and natural cubic splines and a various number of knots for each model. For both subsets of Part One and Two, natural cubic splines with three internal knots at suitable quantiles were found to be the best fit. In contrast, for both subsets of Part Three, the best fit was found using natural cubic splines with just two internal knots at suitable quantiles.

The second research question was addressed using logistic regression to determine the probability of achieving the target reperfusion time for all three parts and both subsets. The same natural spline models identified as the best fit from the above analyses, were then plotted against the estimated probability of achieving the corresponding target reperfusion times. Plotting this curve allowed the identification of 'points of interest' at which the rate of change of the curve's slope was the greatest. The point of interest associated with the highest probability of achieving reperfusion targets was considered the optimal time for all three parts and subsets.

The third research question was addressed using quantile regression to estimate the independent effect specific time points i.e. 'FMC-ECG' time, 'FMC-CCL' time and 'symptom onset-FMC' time, along with other explanatory variables, had on the proceeding time to reperfusion. Interval groups were created for age and the aforementioned specific time points of care time to provide a better understanding of the results. Age was categorised according to the distribution of the continuous data; specific time points of care according to the highest probability time identified and the corresponding 50% probability time identified in research question two. Bootstrap resampling was used to estimate the confidence intervals and standard errors, the method also utilised by Atzema and colleagues. Confidence intervals that did not contain the value of zero were considered statistically significant. All analysis was performed using the programming language R, software version 3.4.3 (2009-2018, Inc.).

3.3 Overview of Study III

The final study in this thesis, Study III, explores the perceived barriers to effective STEMI management as reported by frontline clinicians via a stakeholder survey. The survey was named the **F**rontline c**L**inician survey to **U**nderstand delay in the manage**ME**nt of STEMI or the **FLUME** survey. The first research question is to identify the most commonly occurring barriers to timely STEMI for paramedics and emergency nurses. The second research question is to compare differences in the barriers identified by professional group i.e. paramedics vs emergency nurses, and the third research question is to compare difference by geographical location i.e. metropolitan and regional/rural areas.

3.3.1 Study setting

The Australian state of Victoria was the setting for Study III. The population of Victoria is 6.32 million and approximately, four million people live in metropolitan Melbourne (Australian Bureau of Statisitics., 2019c). There are 40 public hospitals with EDs in Victoria; 23 located in metropolitan and 17 in regional/rural areas (Victorian Agency for Health Information., 2019).

In Victoria, the delivery of STEMI reperfusion strategies varies by geographical location and mode of presentation. All large metropolitan tertiary level hospitals routinely provide a 24/7 primary PCI service. Any STEMI patient self-presenting to these institutions would be immediately transferred to the cardiac catheter laboratory (CCL). For patients presenting via ambulance there is one of two ways they are field triaged: 1) ambulance

presentations who fulfil STEMI 12-lead ECG criteria in the field utilise a pre-hospital notification (PHN) system which activates CCL services prior to hospital; or 2) ambulance presentations who do not have diagnostic ECG changes suggesting STEMI are transported and triaged as usual at the destination hospital. Up until mid-2017 the PHN system was restricted to mobile intensive care ambulance (MICA) paramedics. Recently, advanced life support (ALS) paramedics have also been trained and equipped to acquire and transmit ECGs to all metropolitan hospitals.

In contrast to the metropolitan STEMI services, some Victorian regional hospitals utilise the same PHN system described above for STEMI patients, if primary PCI services are available. Otherwise both regional and rural areas administer thrombolysis as the reperfusion strategy. Since March 2015, MICA paramedics have had the capacity to administer pre-hospital thrombolysis (PHT). However, at the time of the survey these established regional/rural STEMI systems were in a state of flux. Under the auspices of the Victorian ambulance service, all regional/rural ALS paramedics were in the process of being trained and equipped to administer PHT which was completed by March 2018. This process was also supported by a Cardiology consult hotline that was operational from April 2017. Additionally, one regional area of Victoria was trialling an app-based communication tool for STEMI and stroke management to improve timely processes of care.

3.3.1 Study participants

Two organizations were approached to participate in the FLUME survey. The first, Ambulance Victoria (AV), the sole organization that employs all 3450 operational paramedics in Victoria; 520 Mobile Intensive Care Ambulance (MICA) paramedics and 2930 Advanced Life Support (ALS) paramedics. The known geographical location of operational paramedics offered by the ‘People and Culture Division’ of AV is 59% metropolitan and 41% regional/rural operational employees. The second, the College of Emergency Nursing Australasia (CENA); a professional organization representing emergency nurses across Australia. Since the target state was Victoria, survey distribution was restricted to the organization of AV and the 452 financial Victorian members of CENA. Recruitment via CENA was chosen because of the difficulties in accessing the total target population of Triage nurses in Victoria. As the required ethical governance procedures to achieve this would have exceeded the time restraints to conduct this study.

3.3.2 Ethics approval

The survey was granted approval from La Trobe University College Human Ethics Committee [approval number S17-011], Ambulance Victoria Research Committee [approval number R17-003], and the Research Committee of the College of Emergency Nurses Australasia (Victorian Branch) [CENA/RC/2017/03]. *(See appendices 3,4,5)*

3.3.3 Survey development

The survey tool was developed by a research team of experienced cardiac nurses, health service evaluators, health science researchers and interventional cardiologists. Two of these team members had extensive experience in survey methodology, administration and analysis. The design of the survey combined clinical experience, known literature of the barriers to timely STEMI management and utilisation of the Theoretical Domains Framework (TDF).

The TDF has emerged from the 'implementation science' movement; a study of methods that promote the routine and systematic uptake of research findings into practice to improve quality and effectiveness of health care and services (Eccles & Mittman, 2006). The TDF draws on psychological theory relevant to the implementation of evidence based practice, and simplifies these theories by categorizing them into key behaviour change domains (Francis, O'Connor, & Curran, 2012; Michie et al., 2005). The TDF was first reported by Michie et al., (2005) as a primary framework to understand the behaviour change processes that are inherent in the implementation of evidence based practice (Michie et al., 2005). The TDF captures 128 explanatory constructs derived from 33 psychological theories. An expert consensus approach involving behavioural scientists was employed to condense these theories into 12 domains initially and, more recently, 14 domains, that explain behaviour change (Cane, O'Connor, & Michie, 2012; Michie et al., 2005). The current 14 domains are: "knowledge"; "skills"; "social/professional role and identity"; "beliefs about capabilities"; "optimism"; "beliefs about consequences"; "reinforcement"; "intentions"; "goals"; "memory", "attention and decision processes"; "environmental context and resources"; "social influences"; "emotion"; and "behaviour regulation" (Cane et al., 2012). The validity of the TDF has been reported in process evaluations (Cane et al., 2012; Curran et al., 2013), along with its use in survey development for implementation problems (Atkins et al., 2017). The TDF does not postulate identification of testable relationships between behavioural elements, but rather provides a theoretical lens through which to view the cognitive, affective, social and environmental influences on health professional behaviour (Atkins et al., 2017). According

to Atkins et al., (2017) using the TDF for survey development is a three-step process: firstly, the target behaviour needs to be selected and specified; secondly, these behaviours need to be specified in terms of who needs to do what, when, where, how and with whom; and thirdly, the attributes of the target behaviour such as complexity, action sequences and interdependence of team-level behaviours need to be established (Atkins et al., 2017).

The approach recommended by Atkins and colleagues was not suitable in the development of the FLUME survey. The target behaviour of STEMI management is a complex three-way interaction between a presumed STEMI patient, a frontline clinician and a system of care operating across heterogenic organisational delivering boundaries, with health institutions tailoring STEMI processes to their internal resources. Therefore, the TDF was applied at a broader level in this study, using it as a sensitising tool to ensure the survey comprehensively represented possible barriers to timely STEMI management that health professionals may experience.

The final product was a 79-item response survey that consisted of a demographic section, five distinct areas of interest, and open-ended questions. The demographic items included professional membership, geographical location, highest qualifications; years of experience and number of STEMI's managed per month. Open-ended questions were offered allowing respondents to elaborate on their answers and/or raise issues not identified in the survey.

The five survey sections had 56-items covering: i) the presence of workplace policies and procedures (10-items); ii) respondent's commitment to guidelines (3 survey-items); iii) proportion of time organizational/environmental characteristics affect timely management of STEMI (15-items); iv) respondent's levels of confidence to recognise and response to suspected STEMI (17-items); and v) points of communication affecting timely management of STEMI (11-items).

The first survey section covering 'policies and procedures' provided respondents the opportunity to confirm the existence of policies and procedures in their workplace, with response options of "Yes', 'No', 'NA' (not applicable) or 'Don't know'. These questions were constructed around position statements published by relevant professional associations (e.g., NHFA and AHA) and the reviewed literature reflecting the influence organisational culture had on the delivery of STEMI management (Bradley, Curry, et al., 2006; Bradley, Herrin, et al., 2006; Drew et al., 2011; Maddox & Ho, 2017; Nam et al.,

2014; National Heart Foundation of Australia., 2012; Rokos et al., 2009; Tubaro et al., 2011).

The remaining survey sections utilised a visual analogue scale (VAS) for individual item responses. This particular type of scale provides a measurement of perception across a continuum scale "to capture the dynamic and potentially asymmetrical context in which the capacity to record a response cannot be directly measured" (Wewers & Lowe, 1990). The VAS was considered appropriate for capturing responses to the complex constructs in the survey, including personal commitment, estimates of the proportion of time an event was observed to take place, and confidence to undertake a range of tasks. Using a VAS for the different survey sections resulted in scores with the same range (0-100), which makes it easier for analysis. A 10cm line with an appropriate verbal descriptor at each end, and a moveable marker set at 0 to start, was offered to survey respondents.

The second survey section asked participants about their commitment to the STEMI management guidelines, in particular how achievable they perceived the Australian performance targets for 'time to ECG' and 'time to reperfusion' to be (Chew et al., 2016). This section used a VAS with the verbal descriptors "0% of the time" and "100% of the time" to measure the participants' response.

The third survey section also utilised a VAS with labels anchoring each end: "0% of the time" and "100% of the time". This section included statements about the barriers to timely STEMI management derived from clinical experience and found in the literature review, such as under-triaging/mis-dispatch, overcrowding, time of presentation and the environmental context frontline clinicians operate in (Al-Zaiti et al., 2013; Atzema et al., 2009; Coventry et al., 2013; Fourny et al., 2011; Jones et al., 2014; Kulstad & Kelley, 2009; Lindstrom et al., 2014; Pines et al., 2009; Ryan et al., 2016; Schull et al., 2004; Shen & Hsia, 2011).

The fourth and final survey section measured participants' confidence to recognise and respond to suspected STEMI patients using a VAS labelled at each end "0% confident" to "100% confident". These statements were constructed based on the reviewed literature about factors that influence rapid clinical decision making in critical care environments (Bucknall, 2003), in particular, interpretation of unique ECG patterns, along with symptom variation and incongruence in STEMI presentation (Clark et al., 2010; Garvey et al., 2016; Park et al., 2014; Pope et al., 2000; Thygesen et al., 2018).

Survey development also included scrutiny of the wording of questions, particularly for VAS scale items, to ensure wording contained one concept and thus a consistent unipolar interpretation of response could be made (Streiner & Norman, 2008). Furthermore, item response analysis took place to guide decisions about item retention, modification and deletion ensuring alignment with the study aims (Polit & Beck, 2012). Prior to distribution the survey underwent cognitive testing, to establish content validity (Levine, Fowler, & Brown, 2005). A convenience sample of 12 experienced paramedics and Emergency Nurses provided feedback on clarity of language, comprehension, appropriate length and structure of the survey items. Minor modifications were made where necessary.

3.3.4 Survey procedure

The survey was on-line and generated using Qualtrics© software. An email invitation was sent to all Victorian members of CENA and operational paramedics of AV, with a participant information statement (PIS) and electronic link to the Qualtrics© platform. Commencing the survey was deemed to indicate consent. Recruitment strategies included posters and use of social media advertising the FLUME survey. An incentive of a $250 VISA debit card prize draw was employed to maximize response rates. To maintain anonymity participants were redirected to a separate link at the end of the survey to voluntarily enter the prize draw. The survey data collection period was over a five-month period, between the dates August 1, 2017 to December 15, 2017.

3.3.5 Statistical analyses

Descriptive analyses were undertaken for the demographic questions. Exploratory factor analysis was undertaken on the five distinct sections to explore whether the individual items grouped into types of barriers. The purpose of the factor analysis was to simplify reporting and to enable comparisons between different groups of respondents with fewer repeated tests of significance (Streiner & Norman, 2008). Solutions that provided the most coherent factors with the least duplication of item loadings when analysing sections of the survey items were selected using either principal component analysis (PCA) or principal axis factoring (PAF). The final composition and labelling of the types of barriers were agreed by the research team. Comparison of responses to the types of barriers by professional group and geographical location was undertaken using either parametric or non-parametric testing according to the data distribution. The IBM SPSS Statistics for Mac, Version 24 (IBM Corp., Armonk, N.Y., USA) was used for this statistical analysis.

Analysis of the open ended questions was undertaken with similar content grouped and coded as themes in line with the approach recommended by Braun and Clarke (Braun & Clarke, 2013). The purpose of this analysis was to confirm that the representation of barriers included in the survey was comprehensive, and to identify any issues not captured.

3.4 Chapter summary

This chapter has outlined the methodology applied to all three studies that form the body of research for this thesis. All three sections have detailed the study site and population, inclusion/exclusion criteria, ethics approval, data collection (Studies I & II), survey development (Study III), and statistical analyses used for each study. Study I and II utilise the same dataset from a single high performing metropolitan hospital but examines this data with different research objectives. Study III uses a voluntary and anonymous online survey of frontline clinicians to establish the barriers to timely management as perceived by frontline clinicians' using a stakeholder survey.

CHAPTER 4: RESULTS FOR STUDY I

4.1 Chapter introduction

This chapter reports the results of the comparison between the European and the Australian and New Zealand performance parameters for STEMI management. As outlined in Chapter One, this study addresses the first research aim of the thesis and is guided by the following three research questions:

1) What proportion of STEMI patients currently meet the updated ESC target time parameters?
2) When discrete groups are formed, what are the differences in clinical characteristics and health outcomes between patients meeting ESC target time parameters versus patients meeting CSANZ target time parameters?
3) What are the predictors of meeting ESC target time parameters?

4.2 Study I (Manuscript)

Australian STEMI patients currently meeting the updated European Society Cardiology (ESC) reperfusion target parameters and the impact on one-year outcomes.

Abstract:

Background: The updated ESC STEMI management guidelines contain two explicit changes to target parameters which are distinct to the existing Cardiac Society of Australia and New Zealand (CSANZ) guidelines. Firstly, time starts from 'first field contact' not 'door time' for patients diagnosed prior to hospital arrival, with the target parameter ≤90-minutes to coronary intervention. Secondly, patients diagnosed upon hospital arrival have reduced target parameters from ≤90-minutes to ≤60-minutes to coronary intervention. This study aimed to determine the percentage of patients achieving the updated ESC target parameters and the impact on health outcomes in an Australian setting.

Methods: A consecutive STEMI cohort of 922 patients at a large tertiary hospital in Australia was analysed. ESC target achievement was established by recalculating the number of patients presenting with pre-hospital notification (PHN) who accomplished a first 'field' medical contact to balloon time of ≤90 minutes; and determining the number of hospital presenters with a door to balloon time of ≤60 minutes. Discrete target parameter groups were formed from 709 patients: 'achieved ESC targets' (n=342); or 'achieved CSANZ targets only' (n=367). Logistic regression identified characteristics associated with meeting the ESC target times. Cox proportion hazard modelling determined predictors of one-year mortality.

Results: The percentage of STEMI patients in our Australian cohort meeting the updated ESC reperfusion targets was 37% compared to 77% for the CSANZ targets. Logistic regression found that those who achieved the ESC targets were more likely to be younger (OR 0.98, 95%CI 0.97-0.99; *p=0.04 per year*), present during business hours (OR 7.90, 95%CI 5.27-11.97; p<0.001), present with PHN (OR 5.25, 95%CI 3.45-8.00; p<0.001), not intubated prior to Cardiac Catheter Laboratory arrival (OR 6.5, 95%CI 1.4-30.7; p=0.02), and have a trans-radial approach (OR 1.75, 95%CI 1.16-2.64; p<0.01). Achieving ESC performance targets was not an independent predictor of one-year survival (HR 2.35, 95%CI 0.82-6.73; p=0.11).

Conclusion: The updated ESC targets are currently very difficult to achieve in Australia, particularly out of business hours and without pre-hospital activation of destination reperfusion services. In this cohort, achieving the ESC parameters for timely treatment conferred no significant benefit in one-year survival when compared with the current CSANZ timeframes.

Keywords:

ST-Elevation Myocardial Infarction; Time to Treatment; Guideline Adherence

Main Text

Introduction:

For nearly two decades door to balloon time (DTBT) has been the standard parameter of performance for emergent percutaneous coronary revascularization (PCI) in ST-segment elevation myocardial infarction (STEMI). This parameter acknowledges the well-recognized time sensitive nature of restoring epicardial coronary blood flow, with delay being a major determinant of morbidity and mortality [1-4].

The current CSANZ guidelines [5] refer to a ≤60-minute time to treatment parameter as ideal, particularly for patients who present within one hour of symptom onset. However, the key recommendations for Australia espouse an overall ≤90-minute target for DTBT.

In conjunction with the integration of evidence-based reperfusion parameters in the STEMI management guidelines, the last two decades of literature has reflected an increased analysis of strategies to improve access to timely treatment. Exploration of system based determinants have offered practical recommendations at a local level [6]. A well-known recommendation is the integration of pre-hospital notification (PHN) systems by paramedic services into existing hospital processes of care, which has led to substantial and sustained improvements in DTBT [7]. However, the performance parameter for this mode of presentation commences only when the hospital door is reached and does not account for potential paramedic delay that may occur prior to hospital arrival. This gap has been clearly addressed with the updated ESC STEMI management guidelines [8].

In 2017, the ESC made explicit changes to their guidelines [8]. The term 'DTBT' was removed and replaced with first medical contact (FMC), which is defined as either FMC to a hospital or 'Field' FMC when a STEMI diagnosis could be confirmed by an ECG prior to hospital arrival. The performance target was altered in two ways according to mode of presentation: patients presenting to hospital were given a reduced target of ≤ 60 minutes; and PHN patients diagnosed by a field ECG were given a target reperfusion time of ≤ 90 minutes starting from 'field' FMC. Whilst not implicitly stated, it is assumed these were evidenced by literature demonstrating that delay from first contact with the health care system; either in the field or hospital, was independently associated with increased long-term mortality [9, 10].

To our knowledge there is no literature directly comparing the ESC and CSANZ performance targets. Therefore, it is unclear if these updated ESC reperfusion targets are achievable in Australia, and whether attaining these target parameters has a positive impact on outcomes when compared to the existing CSANZ targets parameters.

The primary aims of this study were to;

1. Calculate the percentage of STEMI patients that currently achieve the updated ESC reperfusion targets.
2. Determine the clinical characteristics that are associated with attaining the ESC reperfusion targets.
3. Determine whether achieving ESC targets has a beneficial effect on outcomes including one-year survival.

Methods:

Cohort and Setting

We evaluated a cohort of 922 consecutive STEMI patients between July 2009 and December 2017 at a single tertiary hospital that performed primary PCI as the exclusive treatment strategy for STEMI. This time period marked the operationalization of a pre-hospital notification (PHN) system integrated into an existing hospital rapid facilitation process of care for STEMI. Exclusion criteria comprised of patients with normal coronary angiography, inter-departmental and inter-hospital STEMI transfers, or where no coronary intervention was required.

Data Collection and Ethics Approval

Our study utilised a database with institutional HREC approval and conformed to relevant ethical guidelines. This database maintained by the Cardiac Catheter Laboratory (Cath Lab) prospectively captures STEMI management performance as part of an ongoing quality improvement program. Baseline clinical and procedural characteristics, with specific time point data along the STEMI management continuum are recorded for all patients presenting to the Emergency Department (ED).

'Symptom onset' is recorded as the first documented time from either the paramedic notes or hospital records. 'Door time' is documented as arrival time for PHN STEMIs, or Triage time for hospital presenting STEMIs from the electronic hospital medical record. 'First ECG time' is documented as the recorded field or hospital 12 lead-ECG. 'Cath Lab Activation time', 'Cath Lab arrival time' and 'balloon/device time' are documented prospectively as the process of care is activated and the patient proceeds to coronary intervention. Time of presentation is stratified by arrival to hospital within operating business hours (Monday-Friday; 08:00hrs-18:00hrs) or out of these operating business hours.

Symptomology, comorbid condition and outcomes are recorded for each STEMI patient. Typical or atypical symptomology is defined as per the ten descriptions of Shin *et al.* [11]. Typical: chest pain, pressure or discomfort; diaphoresis; shoulder/arm pain; jaw/neck pain; or dyspnoea. Atypical: back pain; tiredness/fatigue; gastro-intestinal (GI) distress- such as nausea, epigastric or vomiting; palpitations; dizziness/faintness; or paroxysmal nocturnal dyspnoea. Fast onset or slow onset of symptomology is defined as per O'Donnell *et al.* [12]. Fast onset: as the main symptom of chest pain tightness/discomfort that is sudden continuous and severe. Slow onset: as any typical or atypical symptom that is gradual or intermittent which may become continuous; or mild which may gradually become intense.

Clinical risk profile is assessed for each patient using the Thrombolysis in Myocardial Infarction (TIMI) risk score. This validated composite scoring system takes into account age, haemodynamic status, cardiac risk factors, symptom onset, location of infarct, and Killip class to predict 30-day mortality and can be considered a proxy for comorbid condition [13].

Procedural characteristics are recorded prospectively and include, type of arterial access i.e. trans-radial or trans-femoral, insertion of intra-aortic balloon pumps (IABP) pre or post reperfusion, and 'TIMI grade flow' 0 - 3 pre and post reperfusion i.e. TIMI 0 flow representing total occlusion of vessel, through to TIMI 3 flow representing normal perfusion [14].

Health outcomes prospectively recorded are peak creatine kinase (CK units/litre), length of hospital stay, left ventricular ejection fraction (LVEF) as assessed by transthoracic echocardiogram (TTE) up to six weeks post index admission, and in-hospital mortality. Mortality rates out to one-year were obtained from two registries; the Melbourne Interventional Group (MIG) outcome registry from the year 2009-2011 and the Victorian Cardiac Outcomes Registry (VCOR) from 2012-2017 [15, 16].

In order to determine STEMI performance according to the updated ESC targets, recalculation of timepoint data for the PHN cohort was required. 'Field first medical contact' time was located and documented from a retrospective chart review of the paramedic notes for all PHN presentations. Distance in kilometres to the treating hospital for these patients was also recorded to provide context to the overall field to reperfusion time.

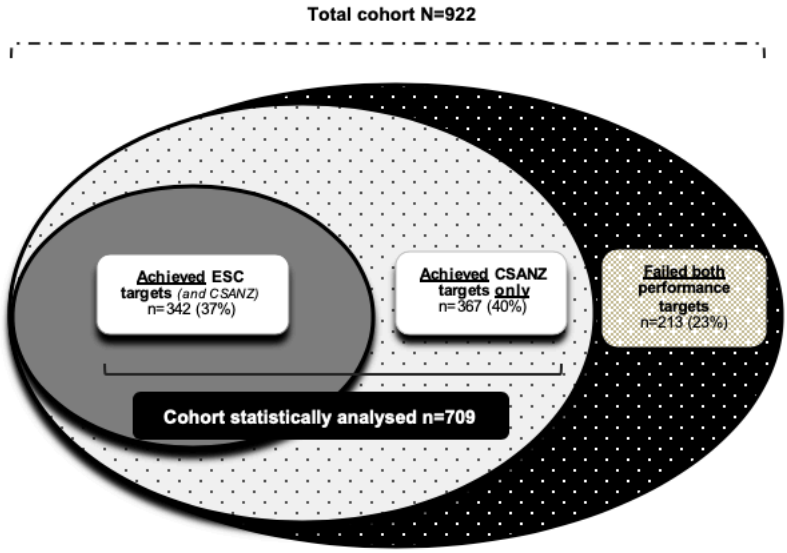
Statistical Analysis

There were several methods utilised to address the research aims. Firstly, the overall percentage of target time achievement for both sets of guidelines was determined for the

total cohort of 922 STEMI patients, using existing and retrospectively applied time point data.

Secondly, the 709 patients who achieved reperfusion targets were separated into discrete groups; patients who achieved ESC targets (n=342), or patients who achieved CSANZ targets only (n= 367). By definition it was possible to achieve ESC targets and CSANZ targets *(see Figure 1).*

Figure 1: Venn diagram to illustrate the formation of discrete groups analysed.



Categorical and continuous variables were reported. Univariate analysis was undertaken using Chi square analysis, Student's t-test or Mann-Whitney *U* test where applicable. The Kaplan-Meier method was used to estimate cumulative incidence of all-cause mortality out to one year between target groups using the log rank test. Two methods of multivariate analyses were performed; logistic regression and cox proportional hazard ratio modelling. Variables with p values <0.10 identified in univariate analysis were entered into the separate models, respectively, to determine independent predictors of achieving ESC reperfusion targets and survival out to one-year. Both regression analyses adjusted for the same four variables; age, TIMI risk >5, cardiac arrest and intubation prior to Cath Lab arrival. Statistical analysis was performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp., Armonk, N.Y., USA). Statistical significance was set at $p<0.05$.

Results:

The percentage of STEMI patients in this cohort achieving the updated ESC reperfusion targets was 37% while 77% met current CSANZ targets (Table 1). When stratified by 'time', 'mode' and both, 'mode and time of presentation', ESC targets were achieved in fewer cases across all categories. Of note, only 5% of hospital presentations arriving out of business hours achieved the ESC target parameter of ≤60 minutes.

Table 1: Performance of total cohort using CSANZ and ESC target definitions.

	Number of patients	Achieved ESC targets ∞ *n (%)*	Achieved CSANZ target Ω *n (%)*
Overall	922	342	709 (77%)
Time of presentation			
In business hours (Mon-Fri 08:00hrs -18:00hrs)	358	211	308 (86%)
Out of business hours (Mon-Fri 18:00hrs-08:00hrs, PH) ß	564	131	401 (71%)
Mode of presentation			
Hospital presentation *(self or regular ambulance)*	441	79 (18%)	253(57%)
Pre-Hospital notification presentation	481	263	456 (95%)
Mode and Time of presentation			
Hospital presentation in business hours	180	30 (43%)	130 (72%)
Hospital presentation out of business hours	262	13 (5%)	123 (47%)
Pre-Hospital notification in business hours	178	145	178 (100%)
Pre-Hospital notification out of business hours	302	118	278 (92%)

∞ *Target parameters: a) hospital presentation FMC-reperfusion ≤60 mins;* ***or*** *b) field FMC-reperfusion ≤90 mins;*

Ω *Target parameter: Door-Balloon Time ≤90 mins for* ***all*** *STEMI presentations*

ß *Public Holidays*

Table 2 compares the clinical characteristics of patients who attained ESC versus CSANZ reperfusion targets. Patients who met ESC targets were more likely to present during business hours, present to hospital with PHN, have trans-radial access, and have a TIMI 0 flow pre-intervention. These same patients were less likely to have a TIMI risk score > 5, cardiac arrest or intubation prior to Cath Lab arrival.

Table 3: Logistic regression modelling predictors of achieving ESC targets.

	Odds Ratio	Confidence Intervals 95%		p value
		Lower	*Upper*	
Age (years)	**0.98**	0.97	0.99	***p=0.04***
Presentation in business hours	**7.90**	5.27	11.97	***p<0.001***
Pre-Hospital Notification presentation	**5.25**	3.45	8.00	***p<0.001***
Triage Score >2	0.86	0.27	2.76	*p=0.79*
Cardiac arrest prior to Cath Lab arrival	0.71	0.31	1.62	*p=0.42*
No intubation prior to Cath Lab arrival	**6.5**	1.4	30.7	***p=0.02***
Known Diabetes	1.5	1.00	2.23	*p=0.05*
TIMI risk score >5	0.63	0.38	1.04	*p=0.07*
Trans-radial access for reperfusion	**1.75**	1.16	2.64	***p<0.01***
Coronary flow TIMI 0 prior to reperfusion	1.45	0.96	2.21	*p=0.07*

Adjusting for age, cardiac arrest or intubated prior to Cath Lab, TIMI risk >5. Overall model N=683; X^2 =205.547; df=10; p<0.001.

Table 4 presents the time-point analysis between reperfusion target groups. Due to divergent definitions between the two sets of guidelines, analysis was restricted to only four timeframes and not included in any multivariate regression modelling. Patients who met ESC targets achieved shorter times in all four measurable timeframes: “Symptom onset-Door”; “Door-Cath Lab”; “Cath Lab-Balloon”; and “Symptom onset-Balloon”.

Table 4: Time points of care# stratified by reperfusion target groups.

	Achieved ESC targets *(n=342)* median *(Q1-Q3)*	Achieved only CSANZ targets *(n=367)* median *(Q1-Q3)*	p value
Symptom to Door Time *(minutes)*	108 (72-237)	**122 (83-264)**	***p=0.03***
Door to Cath Lab Time *(minutes)*	12 (5-22)	**37 (24-48)**	***p<0.001***
Cath Lab to Balloon Time *(minutes)*	25 (21-30)	**32 (26-41)**	***p<0.001***
Symptom to Balloon Time *(minutes)*	149 (111-272)	**190 (150-325)**	***p<0.001****

These variables were not used in multivariate analysis. *Statistically significant

Health outcomes associated with attaining the ESC targets are displayed in Table 5. There was a shorter length of stay in hospital for patients who met the ESC targets, however no statistically significant differences were found for mortality out to one-year. Figure 2 displays the Kaplan Meir analysis of one-year survival. No statistical significance was found between target groups using the log rank test (p=0.07).

Figure 2: Kaplan Meier survival curves stratified by reperfusion target group.

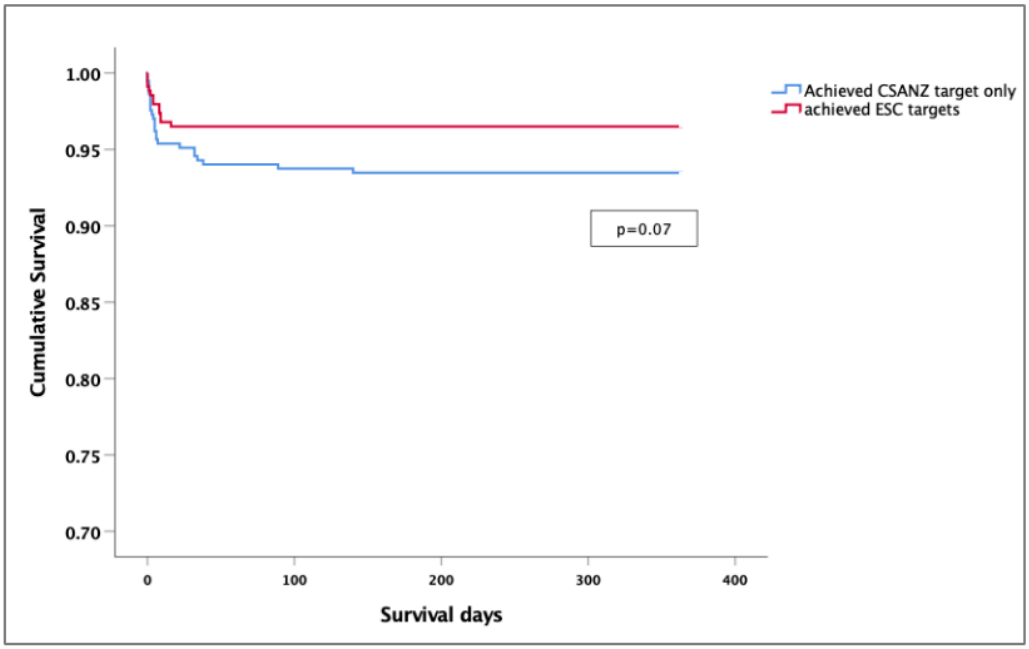


Table 6 displays the results of the cox proportional hazard modelling undertaken to determine whether achieving the ESC targets improved survival at one-year. The final model demonstrated achieving the ESC targets had no statistically significant impact on mortality rates at one year (HR 2.3, 95%CI 0.82-6.73; p=0.11).

Table 6: Cox proportion hazard modelling predictors of one-year mortality.

	Hazards Ratio	Confidence Intervals 95%		*p value*
		Lower	*Upper*	
Age (years)	1.02	0.98	1.04	*p=0.12*
Known Diabetes	1.03	0.43	2.42	*p=0.96*
Presentation in business hours	1.10	0.47	2.55	*p=0.83*
Pre-Hospital Notification presentation	1.45	0.70	3.02	*p=0.32*
Cardiac arrest prior to Cath Lab arrival	1.27	0.16	9.80	*p=0.82*
Intubated prior to Cath Lab arrival	**21.22**	2.26	199.19	***p<0.01***
Triage Score >2	1.86	0.21	16.16	*p=0.57*
TIMI risk score >5	**7.89**	2.80	22.57	***p<0.001***
Trans-radial access for reperfusion	0.75	0.24	2.32	*p=0.62*
Coronary flow TIMI 0 prior to reperfusion	1.27	0.46	3.48	*p=0.66*
Length of Stay (days)	**0.88**	0.80	0.97	***p=0.04***
Achieved ESC performance targets	**2.35**	**0.82**	**6.73**	***p=0.11***
Symptom to balloon time in minutes	1.00	0.99	1.00	*p=0.27*

Adjusting for age, cardiac arrest or intubated prior to Cath Lab, TIMI risk >5. Overall model N=672; X^2 =287.26; df=13; p<0.001

Discussion:

This study compared the existing CSANZ definition to the updated ESC definitions of timely STEMI treatment and found timely treatment was achieved in this cohort 77% vs 37% respectively. This highlighted a marked reduction in the ability to deliver timely treatment according to the ESC guidelines. To our knowledge, our study is the first detailed application of ESC guidelines to an Australian STEMI population. A recent scientific letter did find that only 36% of STEMI patients met a 60 minute door to balloon time if they presented to hospital within one hour of symptom onset [17].

We found independent predictors of achieving ESC targets were younger age, presentation during business hours, PHN presentation to hospital, no intubation prior to Cath Lab arrival, and trans-radial access for reperfusion. The majority of patients in this real-world cohort did not have these favourable attributes, and likely explain the very low rate of meeting ESC targets. These findings affirm the current literature that report particular clinical presentation and procedural characteristics favour timely STEMI treatment [18-25]. It is very reassuring to find that radial access is associated with more rapid reperfusion times, given the dramatic increase in radial PCI use in Australia [26].

Importantly, our single site study found achieving ESC targets did not independently predict improved one-year survival. The lack of effect that shorter reperfusion times have on mortality has been reported by other investigators. Menees *et al.,* analysed 96,738 patients undergoing PCI for STEMI, and found that over a four-year period time to treatment improved but in-hospital mortality (adjusted for age >75 years, anterior STEMI and cardiogenic shock) remained virtually unchanged [27]. In contrast, Nallamothu *et al*., in a larger retrospective study and using the same registry data over a longer period of time refuted Menees's viewpoint. Nallamothu *et al.,* argued the lack of association between shorter reperfusion times and unchanged mortality rates at an individual level reflect the changing patient population receiving primary PCI; i.e. patients are older and have higher comorbid risk, as techniques and processes have evolved [28].

While our study reports ESC targets are difficult to achieve, these updated guidelines importantly capture pre-hospital notification delay paramedics potentially experience in the field prior to hospital arrival. This mode of presentation is an established system of care for most Victorian metropolitan tertiary institutions, and in our cohort contributed to over 50% of STEMI presentations. We demonstrated this subgroup of patients had outstanding performance when using the CSANZ definition, achieving targets 95% of the time. However, when ESC definitions were applied this dropped to 55%. We suggest the way time to reperfusion is currently measured in Australia for PHN STEMI patients distorts

performance, prevents direct comparison by mode of presentation to hospital, and misrepresents the continuum of care.

The updated ESC guidelines also reflect the distinctive STEMI networks operational in many European countries. Many have catheterisation laboratory facilities which operate with in-house personnel around the clock, in addition to some paramedic services supported by on-board physicians [29-31]. The European system means that the patient's waiting time for reperfusion services is very low. In contrast, most metropolitan Australian STEMI services have 24/7 Cath Lab access that rely on 'out of business hour' recall. It would be expensive and logistically difficult for Australia to replicate the European system with a cardiology team in-house overnight.

We acknowledge our findings are limited by several factors. The data was observational and derived from a single site cohort. Our findings could be strengthened by analysing a larger cohort across multiple tertiary sites.

Conclusion:

This study analysed a large consecutive STEMI dataset and found that achieving the updated ESC reperfusion targets in an Australian setting is very difficult. Presenting during business hours and with pre-hospital notification were the major independent predictors of achieving ESC STEMI performance targets. Importantly, analysis of this cohort found achieving ESC targets was not an independent predictor of improved survival. Our findings suggest that careful consideration needs to be given as to whether these challenging reperfusion targets should be adopted by CSANZ in Australia's current health care system.

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4.3 Chapter summary

This chapter has reported the results of Study I which was an analysis of a large single site cohort comparing the divergent European and Australian and New Zealand reperfusion targets.

The results indicated that the proportion of STEMI patients in this cohort who met the updated ESC target reperfusion parameters was 37%. The independent predictors of achieving ESC targets were presentation during business hours, and with pre-hospital notification. Importantly, achieving these targets had no independent effect on one-year survival.

The next chapter will report the results of Study II and its three separate parts.

CHAPTER 5: RESULTS OF TIMEPOINT ANALYSIS

5.0 Chapter introduction

The following chapter reports the results of the analysis of specific timepoints from symptom onset through to reperfusion in STEMI management, addressing the second set of research questions for this thesis.

There are three sections to this chapter representing the three parameters of care examined for each subset i.e. “hospital presenters” of “PHN presenters”.

Part One: Time to ECG: is a standalone manuscript reporting the relationship between timepoints ‘FMC-ECG’ and ‘ECG-reperfusion’, along with the calculation of the optimal ‘FMC-ECG’ time associated with the highest probability of achieving the ≤90-minute reperfusion target. In addition, this manuscript identifies the independent effect ‘FMC-ECG’ time and specific covariates has on the proceeding timepoint ‘ECG-reperfusion time’ using quantile regression analysis. Appendix 2 reports the notification of the journal submission.

Part Two: Time to cardiac catheter laboratory (CCL): is included as a separate results section in this conventional chapter. The analysis of the relationship between timepoints ‘FMC-CCL’ and ‘CCL-reperfusion’ is reported, along with the calculation of the optimal ‘FMC-CCL’ time associated with the highest probability of achieving the ≤90-minute reperfusion target. In addition, part two identifies the independent effect ‘FMC-CCL’ time and specific covariates has on the proceeding timepoint ‘CCL-Reperfusion’ time using quantile regression analysis.

Part Three: Time to first medical contact (FMC): is also included as separate results section in this chapter, and again reports the relationship between the specific timepoints ‘symptom onset-FMC’ and ‘FMC-reperfusion’. Calculation of an optimal ‘symptom onset-FMC time’ associated with the highest probability of achieving the 210-minute performance target is presented. In addition, part three identifies the independent effect ‘symptom onset-FMC’ time and specific covariates has on the proceeding timepoint ‘FMC-reperfusion’ time using quantile regression analysis.

5.1 Study II Part One: Time to ECG and reperfusion targets (Manuscript)

TITLE:

An analysis of time to electrocardiogram (ECG) and STEMI reperfusion target times: a single tertiary site prospective analysis.

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ABSTRACT:

Objectives: The evidence supporting the ≤10-minute parameter for receiving a 12-lead ECG from first medical contact (FMC) to diagnose STEMI is limited. Our objective was to examine the effect time to ECG had on STEMI reperfusion target times.

Setting: Large Australian tertiary hospital performing primary percutaneous coronary intervention.

Participants: Consecutive prospective cohort of 922 STEMI patients presenting between July 2009 - December 2017. The cohort was stratified into two subsets: "hospital presenters" or "pre-hospital notification (PHN) presenters" to capture the contemporary ability to diagnose STEMI and activate systems of care prior to hospital arrival.

Primary and secondary outcome measures: Our primary outcome measure was the optimal 'FMC-ECG' time associated with highest probability of meeting the <90-minute target for both subsets. Our secondary outcome measure was the independent effect that 'FMC-ECG' time and explanatory variables of interest had on 'ECG-reperfusion' time for both subsets.

Results: For patients presenting to hospital, we estimated a 'Door-ECG' time of seven minutes was associated with a 60% probability of achieving reperfusion targets. For PHN presenters, we estimated a 'field FMC-ECG' time of six minutes was associated with a 71% probability of achieving the reperfusion targets. For hospital presenters, quantile regression demonstrated a 'Door-ECG' time greater than seven minutes and presenting out of hours were associated with prolonged 'ECG-reperfusion' time. For PHN presenters; field 'FMC-ECG' had no independent effect on ECG-reperfusion time, however an age ≥75 years, presentation out of business hours, intubation prior to cardiac catheter laboratory (CCL), and distance to hospital were associated with prolonged 'ECG-reperfusion' time. Being male was associated with reduced 'ECG-reperfusion' time.

Conclusion: A 'FMC-ECG' time between 6-7 minutes or less was associated with the highest probability of achieving reperfusion targets, depending on presentation mode. Further analysis is required to explore the impact on long term outcomes using a multi-site cohort.

Strengths and limitations of this study

- **Contributes to the limited published evidence recommending a 'FMC-ECG' time of ≤10 minutes.**
- **Examines optimal 'FMC-ECG' time and identifies independent predictors of 'ECG-reperfusion' time.**
- **Replicates a methodology that examined the optimal 'Door-ECG' time for STEMI patients receiving thrombolysis.**
- **Limited by single site data but strengthened by the analysis of a prospective and consecutive cohort of STEMI patients.**

Funding statement:
Lorelle Martin received a post graduate scholarship from the National Health and Medical Research Council (NHMRC), for this research [grant number APP1133322].

INTRODUCTION:

In Australia, chest pain is the most common principal diagnosis for patients presenting to the Emergency Department aged 50-89 years[1]. The 12-lead electrocardiogram (ECG) is the diagnostic tool that confirms the diagnosis of ST-segment elevation myocardial infarction (STEMI). The ECG risk stratifies chest pain or symptoms suggestive of acute coronary syndrome (ACS), in conjunction with a focussed health history and physical examination. On the ACS spectrum, STEMI is a time sensitive and potentially life-threatening condition that can only be diagnosed by the presence of ECG criteria. Rapid ECG diagnosis of STEMI is crucial, along with the immediate initiation of expedited care to restore coronary blood flow. Delay to this process of care increases morbidity and mortality[2-5].

The current ACS guidelines recommend that first medical contact (FMC) to ECG time should be ≤10 minutes for any patient with acute chest pain or symptoms suggestive of myocardial ischemia[6-8].The cardiology peak bodies of Europe and North America define this time parameter as a 'Class 1' recommendation i.e. the highest[7 8]. In Australia the grade of recommendation is categorised as 'Strong' i.e. the maximum[6]. However, the levels of evidence vary between peak bodies; Europe and North America rate the level of evidence as 'Level B' (data derived from large non-randomised trials) and the Australian guidelines acknowledge the limited evidence with a rating 'IIIC' level of evidence (comparative studies without concurrent controls) a rating that provides some support for the recommendation[9].

The parameter 'FMC-ECG' time has remained under-examined in the literature over the last 15 years. The guidelines frequently cite a 2006 study conducted by Diercks et al.,[10] who found STEMI patients with a time to ECG delay ≥10 minutes had an associated increase in adverse effects i.e. recurrent myocardial infarction or death in or out of hospital at 30 days (OR 3.95, 95% CI 1.06-14.72; p=0.04). This data was derived from a chest pain

registry cohort of 7488 patients that examined all ACS conditions, although only 371 (5%) of these patients were classified as STEMI patients.

Additional studies cited in the European and North American guidelines as contributing to the evidence for a ≤10 minute ECG parameter, focus primarily on the more contemporary practice of acquiring an ECG prior to hospital arrival, demonstrating a benefit to STEMI patients in terms of outcomes[11 12].It is unclear, however, whether this benefit is due to the pre-hospital notification (PHN) process itself or the timing of the ECG. A recently published study protocol by Yiadom et al. may elucidate this by examining a multisite retrospective cohort, with the aim to analyse and measure outcomes in the more contemporary practices of STEMI screening and diagnostic performance with results pending[13].

An interesting study by Atzema et al.,[14] identified a 'Door-ECG' time of ≤4 minutes was associated with the highest probability of meeting the benchmark target 'Door-Needle' time of ≤30 minutes in thrombolytic reperfusion of STEMI in hospitals. This multisite retrospective cohort study of 2961 STEMI patients aimed to calculate the most efficient 'Door-ECG' time, and independent predictors of 'ECG-Needle' time. The statistical methodology used by Atzema et al.,[14] used cubic smoothing splines to firstly examine the relationship between 'FMC-ECG' time and 'ECG-Needle' time, and secondly analysed the probability of meeting benchmark targets for thrombolysis based on 'Door-ECG' time. Quantile regression was applied to identify the independent effect the derived 'Door-ECG' time and other explanatory variables had on the proceeding time parameter of 'ECG-Needle' time. They concluded that older age, out of business hour presentation, and particular ECG rhythms were associated with a prolonged 'ECG-Needle' time. Further, male gender, a higher income, presenting with cardiac arrest, arriving by ambulance and high-volume centres were associated with shorter 'ECG-Needle' times.

To our knowledge, the aforementioned methodology of Atzema and colleagues has not been applied to patients receiving percutaneous coronary intervention (PCI) as the primary treatment strategy in STEMI. Primary PCI is considered the gold standard treatment over thrombolysis[15]. The ACS guidelines [6-8] recommend a 'FMC-reperfusion' time ≤ 90 minutes. This parameter acknowledges the time sensitive nature of restoring epicardial blood flow, and reflects the extensive literature demonstrating time delay as a major determinant of morbidity and mortality[2-5].

The objective of this study was to examine the effect time to ECG had on STEMI target times for the reperfusion strategy of primary PCI, using discrete subsets: "hospital presentation" or "PHN presentation", to reflect contemporary systems of care available.

Our research questions was guided by three research questions:

1) What is the relationship between 'FMC-ECG' time and 'ECG-reperfusion' time for both subsets?
2) What was the optimal 'FMC-ECG' time associated with highest probability of achieving the target reperfusion time ≤ 90 minutes for both subsets?
3) What was the independent effect of 'FMC-ECG' time and other explanatory variables on 'ECG-reperfusion' time for both subsets?

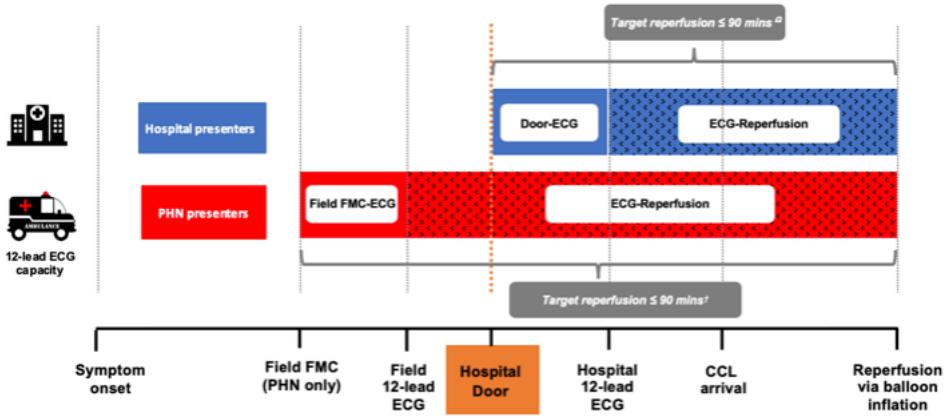
METHODS:

Cohort and Setting

We undertook an observational prospective cohort study of STEMI patients presenting to the Emergency Department (ED) at a single tertiary hospital between July 2009 and December 2017. This time period marked the incorporation of a PHN system into an existing hospital process of care for STEMI. The setting is a metropolitan tertiary hospital that performs primary PCI as the treatment strategy for STEMI patients.

Exclusion criteria applied to the observational prospective cohort were any patient where no coronary intervention was required; inter-departmental and inter-hospital STEMI transfers; and confirmed normal coronary angiography. There were 922 ED patients with STEMI identified. To meet the study aims and perform this particular statistical analysis three additional exclusion criteria were applied; 1) all patients with a 'FMC-ECG' time ≥89 minutes (n=7), as it clearly would be impossible to meet the 90-minute reperfusion target; 2) patients who presented initially with NSTEMI ECG criteria and then developed STEMI ECG criteria while still in ED (n=41), as these patients' adjusted 'Door-ECG' times of zero skewed the timepoint data; and 3) a missed STEMI treated as an extreme outlier (n=1). These conditions were similar to the exclusion criteria Atzema and colleagues applied in their study[14]. The final cohort was 873 patients. The sample was separated into two distinct subsets: 'hospital presentation' (n=393); and 'PHN presentations' (n=480), for the following reason. The current key recommendations of the Cardiac Society of Australia and New Zealand (CSANZ) and American College of Cardiology Foundation/American Heart Association (ACCF/AHA)[6 8] suggest target 'FMC-reperfusion' time is ≤90 minutes starting from hospital arrival ("door"). Based on this definition, our time to ECG analysis for PHN presenters would have a value of zero. This study coincided with a recent divergence in the target reperfusion guidelines between the peak cardiology bodies. In 2017, the European Cardiac Society (ESC) updated their STEMI guidelines[7], and explicitly assigned patients diagnosed prior to hospital arrival (i.e. PHN patients) a reperfusion target of ≤90 minutes from first 'field' medical contact. This new ESC modification to the guidelines accounts for time taken accessing the health system outside the hospital institution, providing us a with a parameter to measure our cohort of PHN presentations in a clinically meaningful way. Figure 1 graphically defines and outlines the measurement of the particular time points analysed in this study.

Figure 1: Time points of care examined for each subset.



Ω CSANZ and ACCF/AHA guidelines for patients diagnosed upon hospital arrival; † ESC guidelines for patients diagnosed prior to hospital arrival.

Data Collection and Ethics Approval

This study was undertaken with institutional HREC approval and conformed to relevant ethical guidelines. Data was derived from a hospital database that prospectively captures STEMI management performance as part of an ongoing quality improvement program. This database uses a standardised protocol to record pre-specified time points of care along the STEMI management continuum. 'Symptom onset' time; 'FMC' time (field or hospital); 'ECG' time (as per ED or ambulance ECG machine); 'CCL arrival' time and 'Reperfusion' time (defined as first balloon inflation or first aspiration device with a thrombectomy/aspiration device). This time point data is regularly audited, ensuring ED and paramedic ECG machines, computer and wall clocks in the CCL are regularly synchronised to correct time and date.

This database also records baseline clinical characteristics and procedural characteristics. For this study we were specifically interested in age; gender; time of presentation ("in hours" was considered business hours of the hospital 08:00hrs-18:00hrs Monday-Friday, and all other hours including public holidays as "out of hours"); mode of arrival (self-presentation or ambulance arrival with or without PHN); assigned Triage score on arrival to ED; typical or atypical symptomology as defined by Shin et al.,[16]; fast onset or slow

onset of symptoms as defined by O'Donnell et al.,[17]; comorbid condition as defined by the Thrombolysis in Myocardial Infarction (TIMI) risk score[18]. All of these variables have been shown to influence timely STEMI treatment[19-26]. In addition, we documented patients who were intubated prior to CCL arrival and whether patients had experienced a cardiac arrest prior to CCL arrival. For PHN presenters only, we recorded field scene postcode derived from the paramedic notes to estimate the distance travelled to the destination hospital.

In-hospital mortality was recorded from hospital records and 12-month mortality was obtained from two registries; the Melbourne Interventional Group (MIG) outcome registry from the year 2009-2011 and the Victorian Outcomes Registry (VCOR) from 2012-2017[27] [28].

Statistical Analysis:

Our statistical analysis replicated the methodology of Atzema et al.,[14] as closely as possible, applying the methodology instead to time points specific to the reperfusion strategy of primary PCI. Our first research question was addressed by modelling the relationship between 'FMC-ECG' (Door or Field) time and 'ECG-reperfusion' time using smoothing splines, a method suited to non-normally distributed continuous data. Smoothing splines fit nonparametric data by joining two or more polynomial curves, with the location of these joins known as knots[29]. Natural cubic splines with three internal knots at suitable quantiles were found to be the best fit for both subsets.

Our second research question was addressed by using logistic regression to determine the relationship between the probability of achieving target reperfusion of ≤90 minutes and 'FMC-ECG' time for both subsets. The same natural cubic spline model described above was applied to 'FMC-ECG' time (Door or Field) and plotted against the estimated probability of achieving the targets. Plotting this curve allowed us to identify the points at which the rate of change of the curve's slope were the greatest. We will refer to these

points as 'points of interest'. The point of interest associated with the highest probability of achieving reperfusion targets was considered the optimal 'FMC-ECG' time for each subset.

Our third research question was addressed by utilising quantile regression to estimate the independent effect 'FMC-ECG' time and other explanatory variables of interest had on 'ECG-reperfusion' time. This method of regression is considered a robust alternative to traditional multiple linear regression, particularly for skewed data, as it models the quantile instead of the mean response on the predictors[30]. Interval groups were created for age and 'FMC-ECG' time to provide a better understanding of these explanatory variables' effect on 'ECG-reperfusion' time. Age was categorised according to the distribution of the continuous data, and 'FMC-ECG' time was categorised according to the logistic regression findings of the shortest FMC-ECG time and the corresponding FMC-ECG time at 50% probability. Bootstrap resampling was used to estimate confidence intervals and standard errors and was the method that Atzema et al.,[14] utilised. For quantile regression, confidence intervals that did not contain the value of zero were considered statistically significant. All time point analysis was performed using R version 3.4.3 (2009-2018, Inc.).

Additional univariate analysis was performed between the subset groups for 'Hospital presenters' and 'PHN presenters'. This was outside the scope of the stated research questions, but we believed it could provide context and explain potential variation in our results. Student's t-test or Mann U Whitney test were used where appropriate for continuous variables and Chi square analysis for categorial variables. Statistical analysis was performed using IBM SPSS Statistics for Mac, version 24 (IBM Corp., Armonk, N.Y., USA). Statistical significance was set at $p<0.05$.

RESULTS:

Table 1 displays the univariate comparison between subset groups for baseline clinical characteristics and outcomes. Statistically significant differences were found between groups. Hospital presenters were more likely to be female, present with atypical and slow onset symptomology, have a TIMI risk score >5, have a shorter 'FMC-ECG' time and achieve the ≤10-minute ECG target more often than PHN presenters. Statistically significant differences were also found for mortality rates. Hospital presenters had higher mortality at one year compared to PHN presenters (11% vs 5%; p<0.001) respectively.

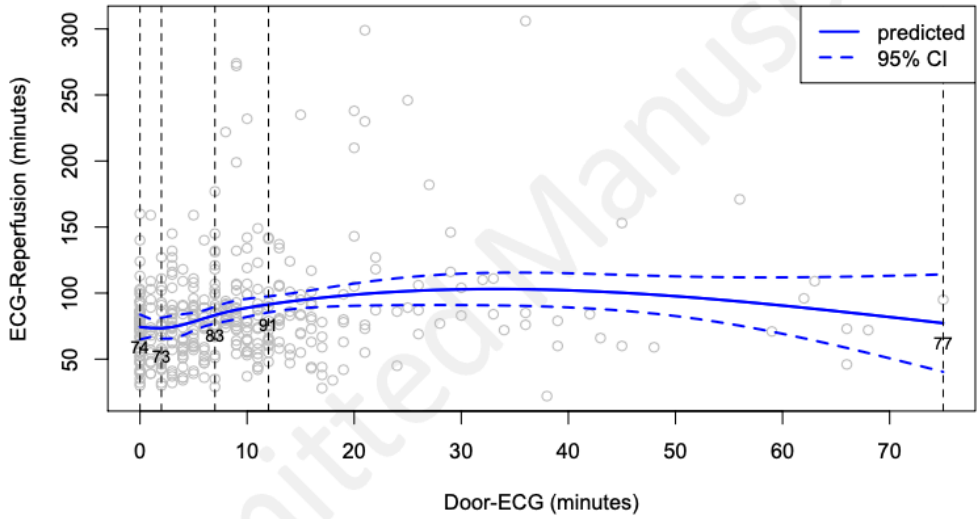
Table 1: Baseline characteristics and outcomes for total cohort

	Hospital presenters (n=393)	**PHN presenters (n=480)**
Age *mean ± SD (years)*	64 ± 13	63 ± 13
Female *n (%)*	**89 (23%)**	**83 (17%) ***
Presentation in business hours *(0800-1800hrs Mon-Fri)*	161 (41%)	180 (37%)
Mode of presentation to hospital		
Self-presentation *n (%)*	158 (40%)	x
Regular Ambulance presentation *n (%)*	235 (60%)	x
Pre-Hospital Notification (PHN)	x	480 (100%)
Distance to hospital (PHN only) median *(Q1-Q3) (km)*	x	9 (6-13)
Atypical symptomology Ω *n (%)*	**76 (20%)**	**35 (7%) *** **
Slow onset symptomology † *n (%)*	**138 (37%)**	**135 (28%) ** **
Assigned Triage score > 2 (Hospital only #) *n (%)*	47 (12%)	X
Cardiac arrest prior to CCL arrival *n (%)*	39 (10%)	50 (10%)
Intubated prior to CCL arrival *n (%)*	32 (8%)	26 (5%)
TIMI Risk score > 5 *n (%)*	**114 (30%)**	**109 (23%) ***
Outcomes		
Achievement threshold of ECG time ≤ 10 minutes *n (%)*	**243 (62%)**	**209 (43%) *****
Achievement threshold of Reperfusion time ≤ 90 minutes *n (%)*	223 (57%)	262 (55%)
'FMC-ECG' time (Door or 'Field) *median (Q1-Q3) mins*	**7 (2-12)**	**11 (6-22)**
ECG-Reperfusion time *median (Q1-Q3) mins*	78 (60-94)	74 (62-91)
'FMC-Reperfusion' time (Door or Field) time *median (Q1-Q3) mins*	87 (67-109)	87 (74-107)
In-hospital mortality *n (%)*	**37 (9.5%)**	**20 (4.1%) ** **
365-day mortality *n (%)*	**43 (11%)**	**24 (5%) ** **

Ω Back pain, fatigue, GI distress, palpitations, dizziness/faintness; † any typical or atypical pain that is gradual or intermittent in nature.
all PHN patients were allocated a triage score of 1on admission. Statistically significant *p<0.05; **p<0.01; ***p<0.001

The relationship between 'Door-ECG' time and 'ECG-reperfusion' time for hospital presenters was non-linear and is shown in Figure 2. In general, the smoothed curve shows a gradual increase to 'ECG-reperfusion' as 'Door-ECG' time increases i.e. from 3-11 minutes, the 'ECG-reperfusion' time increases from 73-91 minutes where the slope flattens and remains constant until 45 minutes. However, there were two points of decline in the slope: from 0-3 minutes the 'ECG-reperfusion' time decreases from 74-73 minutes; and again between 40-75 minutes where the 'ECG-reperfusion' time declines to 77 minutes.

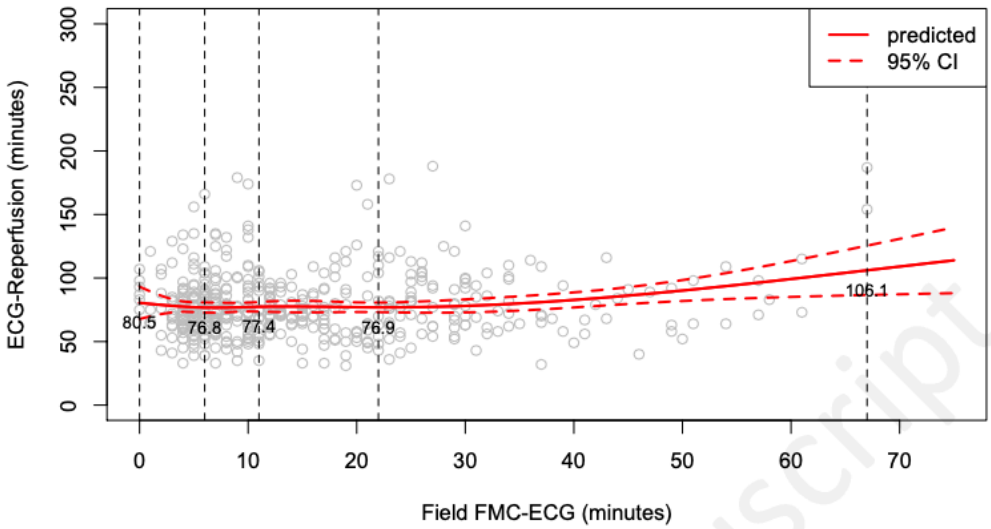
Figure 2: Relationship between time points for hospital presenters*.



*Using natural cubic smoothing splines with three knots at (0.25, 0.50 and 0.75 quantiles).

Figure 3 displays a non-linear relationship between 'Field FMC-ECG' time and 'ECG-reperfusion' time for PHN presenters. The smoothed curve for this data shows a relatively constant 'ECG-reperfusion' time of 77 minutes for 'Field FMC-ECG' time between 7-22 minutes. From 22 minutes onwards, the curve slowly increases to an ECG-reperfusion time of 106 minutes at the maximum 67 minutes mark. Again, we found the model displayed a decline between 0-7 minutes where 'ECG-reperfusion' time decreased from 81-77 minutes.

Figure 3: Relationship between time points for PHN presenters*.



* Using natural cubic smoothing splines with three knots at (0.25,0.50 and 0.75 quantiles).

Figures 4 and 5 plot the predicted probability of achieving the reperfusion target of ≤90 minutes verses 'FMC-ECG' time in minutes according to mode of presentation. The figures also show the calculated 'points of interest' or the points at which the rate of decline visibly begins to speed up or slow down. In mathematical terms, this is the point at which the third derivative is equal to zero. Each plot also displays the FMC-ECG time at the 50% probability point, which was used to create the interval groups in the proceeding quantile regression analysis.

Figure 4 displays the predicted probability of hospital presenters achieving the reperfusion target of ≤ 90 minutes versus 'Door-ECG' time in minutes. There was a relatively linear decline in the probability of achieving targets for a 'Door-ECG' time until 29 minutes, at which point the rate of decline visibly begins to slow down. At 7 minutes we see a point of interest where the probability is 60% (95% CI 51-69%); at 13 minutes the probability declines to 48% (95% CI 42-58%), until 29 minutes where the probability is 11% (95% CI 0-23%). The 50% probability was calculated at 12 minutes. Between 0 and 29 minutes we estimate for every one-minute increase in 'Door-ECG' time there is a decreased probability

of 2.4%, on average, in achieving the reperfusion target. Table 2 displays the rate of actual probability decline in five-minute intervals out to 20 minutes.

Figure 4: Predicted probability of achieving Door to Balloon of ≤ 90 minutes.

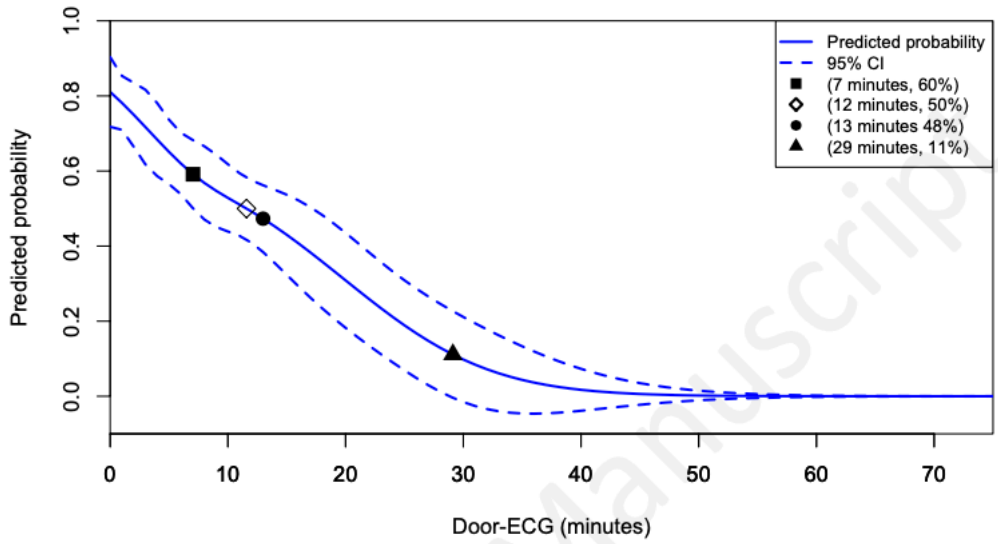


Table 2: Rate of probability decline in five-minute intervals (hospital).

'FMC to ECG' time	Predicted probability of achieving targets
5 minutes	68%
10 minutes	55%
15 minutes	45%
20 minutes	33%

Figure 5 displays the predicted probability for PHN presenters achieving the reperfusion target of ≤ 90 minutes versus 'Field FMC-ECG' time in minutes. Between 0 and 6 minutes, the plot shows a relatively constant predicted probability, staying between 72-75%. At 6 minutes, we see a point of interest where the predicted probability starts to decline more rapidly with a predicted probability of 71% (95% CI 64-79%). A second point of interest can be seen at 32 minutes, where the rate of decline begins to slow down, with a predicted

probability of 19% (95% CI 10-27%). Between these points of interest, we have highlighted the 50% predicted probability of meeting the targets at 18 minutes. Between 0 and 32 minutes, we estimate that for every one-minute increase of 'Field FMC-ECG' time the average probability of achieving the target decreases by 1.8%. Table 3 displays the rate of actual probability decline in five-minute intervals out to 20 minutes.

Figure 5: Predicted probability of achieving field FMC to Balloon of ≤ 90 minutes.

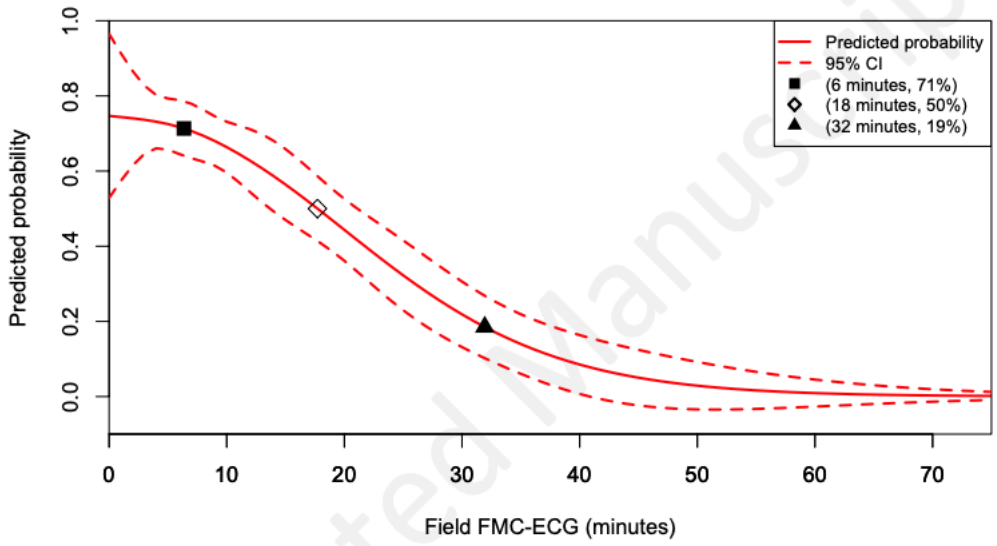


Table 3: Rate of probability decline in five-minute intervals (PHN).

'field FMC to ECG' time	Predicted probability of achieving targets
5 minutes	73%
10 minutes	68%
15 minutes	59%
20 minutes	47%

Figures 6 and 7 display the results of the quantile regression analysis carried out to identify significant predictors of 'ECG-reperfusion' time in minutes.

Figure 6 displays the results of the quantile regression for hospital presenters, showing three statistically significant predictors that were associated with prolonged 'ECG-reperfusion' time. Controlling for all other variables, we estimate the median 'ECG-reperfusion' time for those presenting out of business hours is 25 minutes (95% CI 19-30 minutes) higher than those presenting during business hours. Also, compared with the 'Door-ECG' [0-7) minute group, the (7-12) and (12-75) minute groups have a median 'ECG-reperfusion' time estimated to be 6 and 12 minutes higher respectively (95% CI 0.5-14 minutes and 3-19 minutes).

Figure 6: Quantile regression for hospital presenting patients.

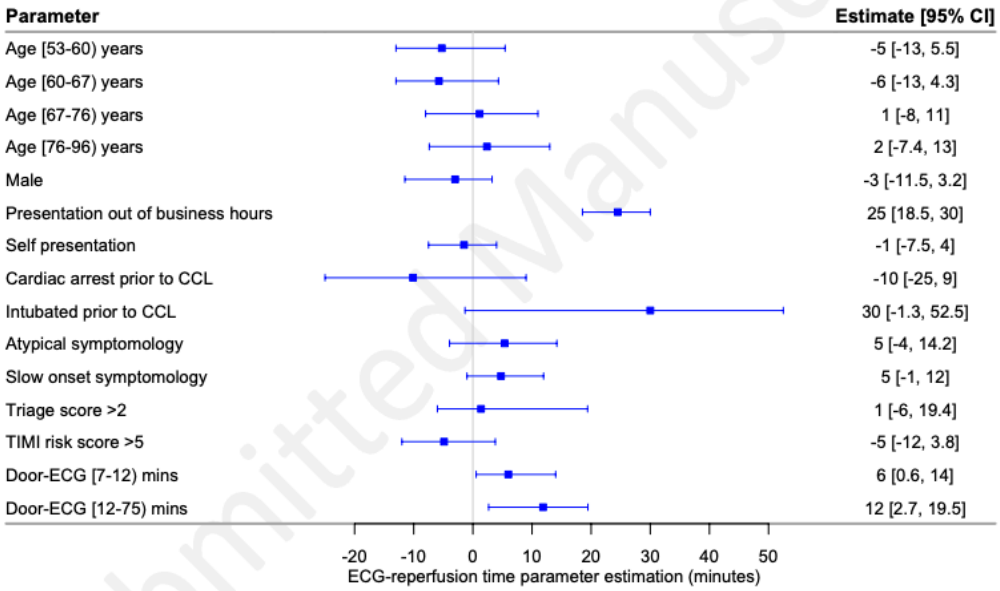
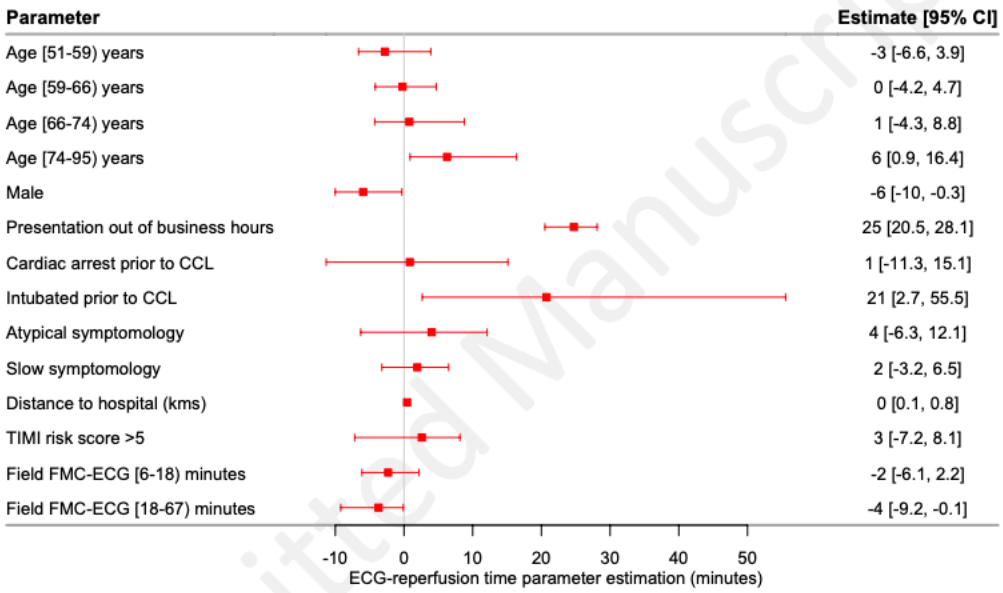


Figure 7 displays the quantile regression analysis for PHN presenters, showing four statistically significant independent predictors associated with higher 'ECG-reperfusion' time and two associated with lower 'ECG-reperfusion' time. Controlling for other variables, we estimate that the median 'ECG-reperfusion' time was increased by the following factors: older age between 74-95 years (when compared with the <51 year age group) by 6 minutes (95% CI 1-16 minutes); presenting out of business hours by 25 minutes (95% CI 21-28 minutes) when compared with presenting during business hours; being intubated

prior to CCL by 21 minutes (95% CI 3-56 minutes); and distance to the destination hospital, by an estimated 1 minute for every 0.5 km to hospital (95% CI 0.1-0.8 minutes). Male gender was associated with reduced 'ECG-reperfusion' time by 6 minutes (95% CI -10 to -0.3 minutes); and interestingly having a 'Field FMC-ECG' time between 19-67 minutes was associated with a reduced 'ECG-reperfusion' time by 4 minutes (95% CI -9 to -0.1 minutes) when controlling for other variables.

Figure 7: Quantile Regression for PHN presenting patients



DISCUSSION:

Our study found the relationship between 'FMC-ECG' and ECG-reperfusion time was non-linear, unsurprising given the data was non normally distributed. We identified the optimal 'FMC-ECG' time associated with the highest probability of achieving the STEMI reperfusion targets was ≤7 minutes for hospital presenters and ≤6 minutes for PHN presenters. These findings were made in the context of a 'time to ECG' achievement threshold of 62% and 57% for hospital presenters and PHN presenters respectively, and a 'time to reperfusion' achievement threshold of 43% and 55% for hospital presenters and PHN presenters respectively (see Table 1). For each minute increase in 'FMC-ECG' time

there was an average decrease in probability of meeting reperfusion targets by an estimated 2.4% and 1.8% for hospital presenters and PHN presenters respectively. Tables 2 and 3 listed the rate of decline in five-minute intervals, which was different for both subsets. This demonstrates substantial room to improve performance targets for both modes of presentation. In comparison, Atzema et al.,[14] found a 4-minute 'Door-ECG' time was associated with the highest probability of achieving the benchmark ≤30 minute reperfusion target for thrombolysis. Atzema et al.,[14] did not report their achievement threshold, however they reported a median Door-ECG time of 8 minutes (IQR 4-15 minutes), which was similar to our hospital presenting cohorts median Door-ECG time of 7 minutes (IQR 2-12 minutes). While we analysed a different reperfusion strategy to Atzema et al.,[14] our estimated optimal 'FMC-ECG' times contrasted their results by providing more time for frontline clinicians to acquire an ECG from first point of medical contact.

For hospital presenters, quantile regression demonstrated that, controlling for other variables, compared with a 'Door to ECG' time between (0-6) minutes, times of (7-12) minutes and (13-75) minutes were associated with a median prolonged 'ECG-reperfusion' time of 6-minutes and 12-minutes respectively (see Figure 6). This finding was in contrast to Atzema et al.,[14] who found no clinically significant effect between these two timeframes. Presenting 'out of business hours' was also an independent predictor of a prolonged 'ECG-reperfusion' time for this subset, with the parameter estimate calculated at 25-minutes of delay. This finding is not unexpected given the reliance on out of business hours recall of the CCL team at our institution. This finding also corresponds with the known literature that out of hour presentations delay time to treatment[31].

For PHN presenters, quantile regression found independent predictors associated with both prolonged and reduced 'ECG-reperfusion' times. Similar to hospital presenters, out of business hour presentation prolonged 'ECG-reperfusion' time by an estimated median

of 25 minutes. Additionally, intubation prior to CCL, age ≥75, and distance to hospital were associated with prolonged 'ECG-reperfusion' time with parameter estimates calculated at 21 minutes, 6 minutes, and <1 minute for per one kilometre from hospital respectively (see Figure 7). These additional independent predictors could be explained by the reality that intubation of a patient often relies on the coordination of other specialities to provide airway support, potentially prolonging time to reperfusion. Older age generally increases the presence of co-morbid conditions, and more time is required to weigh up the benefits of reperfusion versus the potential risk of bleeding complications in an older age group[25]. Distance to hospital was a clinically insignificant finding with the effect of 'ECG-reperfusion' time being 27 seconds.

Interestingly, for PHN presenters, our analysis found two independent predictors that were associated with reduced 'ECG-reperfusion' time; male gender with a calculated parameter estimate of -6 minutes; and counterintuitively a 'field FMC-ECG' time between (19-67) minutes with a calculated parameter estimate of -4 minutes. The influence of gender on time to treatment is well documented in the literature, with females consistently having prolonged time to reperfusion, explained in part by an older age, higher comorbid risk and presenting symptomology[22 26]. The counterintuitive effect of a 'field FMC-ECG' time between (7-18) minutes trending to reduced 'ECG-reperfusion' time and a 'field FMC-ECG' time between (19-67) minutes associated with a reduction in 'ECG-reperfusion' time could be explained by a phenomenon known as cognitive bias. A recent review article by O'Sullivan and Schofield[32] describe cognitive bias in the context of medical errors and the influence this has on decision making skills; in particular 'confirmation bias ' i.e. interpretation of information gained during consultation to fit a preconceived diagnosis, and 'diagnostic momentum' i.e. continuing a clinical course of action instigated by previous clinicians without considering information available. We suggest the same phenomena could act as precipitators of prompt action when clinicians are convinced of the diagnosis and activate processes of care that expedite time to reperfusion from ECG time.

Furthermore, the univariate comparison between subsets, demonstrated that PHN presenters has less atypical and slow onset symptomology, which could also emphasise the impact of cognitive bias.

We acknowledge our study is limited by several factors. Our data is observational and derived from a single site cohort and, while prospective and consecutive, our findings could be strengthened by analysing a larger cohort across multiple tertiary sites. This would improve the generalisability of findings in what we believe to be a robust methodology of analysing time points of care in STEMI treatment. Further, the impact our calculated optimal FMC-ECG timeframes have on mortality and long-term health outcomes remains unanswered. Incorporating health outcomes and applying the same methodology on a larger multisite cohort could offer a significant contribution to the limited published evidence base for the recommended 'FMC-ECG' time.

Our study identified optimal timeframes for 'time to ECG' in the contemporary era of expanded systems of STEMI care with capacity to diagnose STEMI prior to hospital arrival and activate services in the CCL. The optimal 'time to ECG' times identified are achievable in robust systems of care and add to the limited evidence base supporting best practice for time to ECG. Improving the achievement threshold of both 'time to ECG' and 'time to reperfusion' by addressing factors that prolong time to treatment could optimise STEMI target performance and therefore outcomes for STEMI patients who present to hospital directly or via PHN systems of care.

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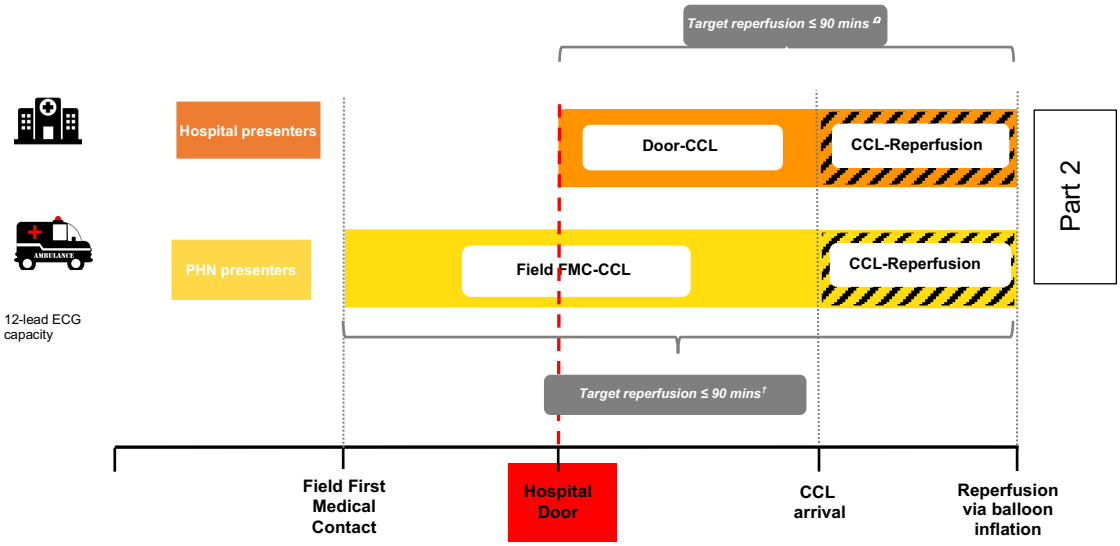
5.2 Study II Part Two: Time to CCL and reperfusion targets.

The following presents the results of Part Two which examines two parameters of interest: the time taken for STEMI patients to reach the cardiac catheter laboratory (CCL) from first medical contact (FMC); and the time taken for reperfusion to subsequently occur in the CCL. Figure 5 illustrates the exact time points measured for each subset i.e. 'hospital presenters' or 'PHN presenters' and defines the reperfusion targets.

Figure 5: *Overview of time points analysed (Study II Part Two).*



Ω CSANZ and ACCF/AHA guidelines for patients diagnosed upon hospital arrival; † ESC guidelines for patients diagnosed prior to hospital arrival

Table 4 displays the univariate analysis of baseline clinical characteristics and outcomes for the time parameter of 'FMC to reperfusion' for Part 2 comparing hospital and PHN presenters. Statistically significant differences were identified. Hospital presenters were more likely to be older, female, present with atypical symptomology, and be intubated prior to CCL. Mortality rates in hospital and at 12 months were higher for hospital presenters than PHN presenters 10% vs 3%; ($p<0.001$), and 11% vs 53%; ($p<0.001$). Hospital presenters took a shorter length of time to arrive in the Cardiac Catheter Laboratory compared to PHN presenters; 47 vs 55 minutes, ($p<0.001$). While hospital presenters took longer for reperfusion to occur once arriving in the Cardiac Catheter Laboratory 31 vs 27 minutes, ($p<0.001$), respectively.

Table 4: *Characteristics of Part Two (n=769)*

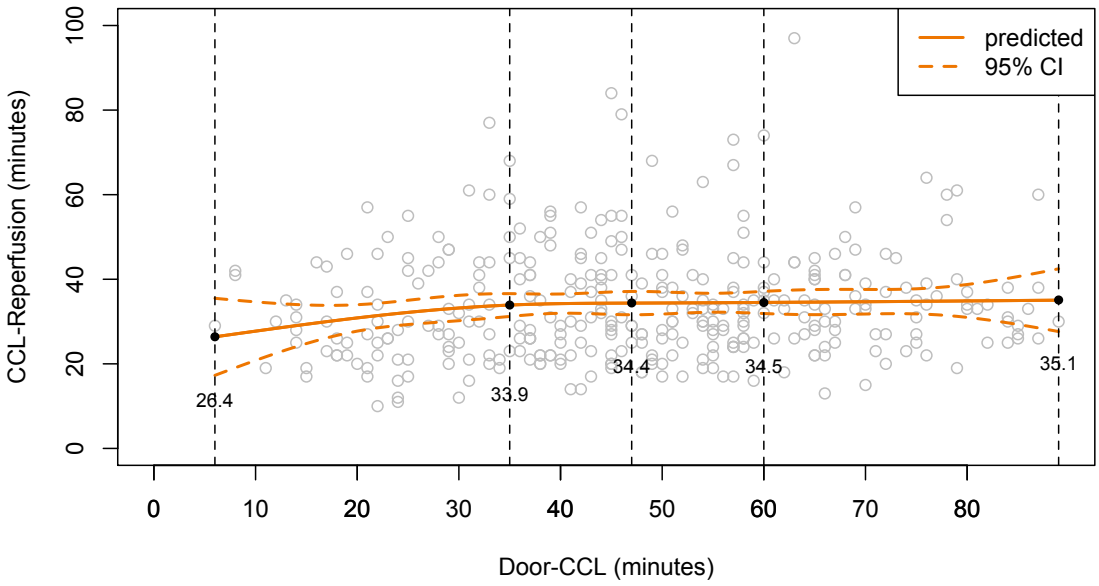
	Hospital presenters (n=341)	**PHN presenters (n=428)**
Age *mean ± SD (years)*	**64 ± 13**	**62 ± 12 ***
Female *n (%)*	**78 (23%)**	**71 (17%) ***
Presentation in business hours *(0800-1800hrs Mon-Fri)*	149 (43%)	175 (41%)
Mode of presentation to hospital		
Self-presentation *n (%)*	143 (42%)	x
Regular Ambulance presentation *n (%)*	198 (58%)	x
Pre-Hospital Notification (PHN) n (%)	x	428 (100%)
Distance to Hospital (PHN only) median *(Q1-Q3) (km)*	x	10 ± 6
Atypical symptomology Ω *n (%)*	**60 (18%)**	**26 (6%) *** **
Slow onset symptomology † *n (%)*	115 (35%)	119 (28%)
Assigned Triage score > 2 (Hospital only #) *n (%)*	31 (9%)	x
Cardiac arrest prior to CCL arrival *n (%)*	30 (9%)	33 (8%)
Intubated prior to CCL arrival *n (%)*	**23 (7%)**	**9 (2%) ** **
TIMI risk >5 *n (%)*	**101 (30%)**	**78 (18%) *** **
Outcomes		
Achievement threshold of reperfusion time ≤90 minutes n (%)	219 (65%)	266 (62%)
'Door or Field FMC– CCL' time *median minutes (IQR)*	**47 (35-60)**	**55 (45-67) *** **
'CCL-Reperfusion' time *median minutes (IQR)*	**31 (25-41)**	**27 (23-36) *** **
Abnormal Left Ventricular Ejection Fraction *n (%)*	45 (18%)	76 (25%)
Length of Stay *median (Q1-Q3) days*	4 (3-5)	3 (3-4)
In-hospital mortality *n (%)*	**33 (9.7%)**	**11 (2.6%) *** **
365-day mortality *n (%)*	**38 (11.1%)**	**14 (3.3%) *** **

Ω Back pain, fatigue, GI distress, palpitations, dizziness/faintness; **†** any typical or atypical pain that is gradual or intermittent in nature.

all PHN patients were allocated a triage score of 1 on admission. Statistically significant *p<0.05; **p<0.01; ***p<0.001.

For hospital presenters the relationship between 'Door-CCL' time and 'CCL-reperfusion' time was linear and is displayed in Figure 6. The smoothed curve defined with three internal knots shows a gradual increase in 'CCL-reperfusion' time as 'Door-CCL' time increases i.e. from 6-47 minutes 'CCL-reperfusion' time increases from 26-34 minutes, where the slope flattens and remains constant between 34-35 minutes until the maximum 'Door-CCL' time analysed of 89 minutes is reached. As the linear relationship suggests there were no points of decline in time, unlike the results in Part One analysing time to ECG.

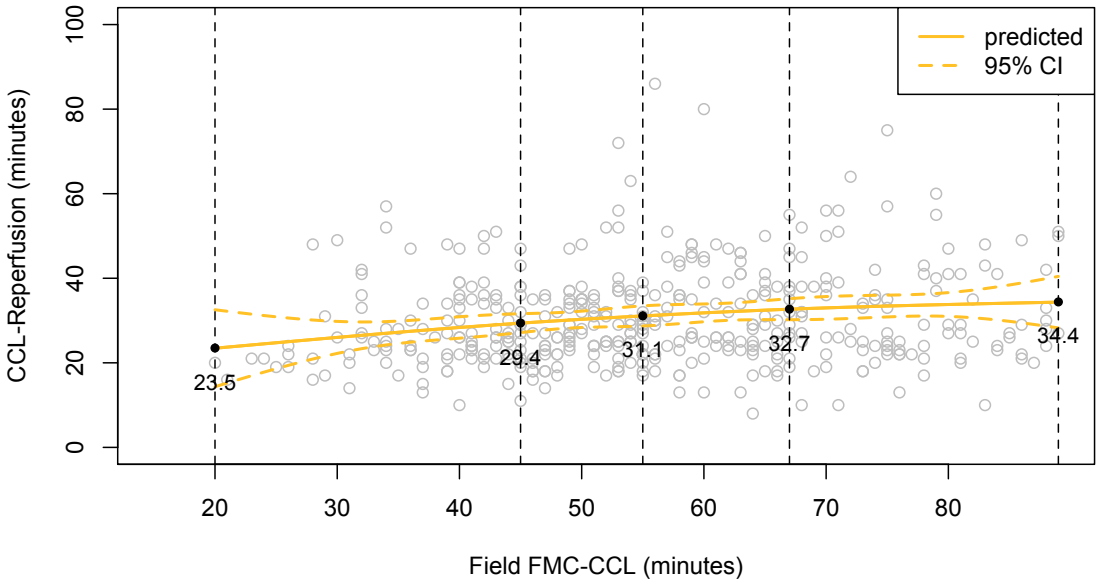
***Figure 6**: Relationship between time points for Part Two (Hospital)* *.*



* Using natural cubic smoothing splines with three knots at 0.25, 0.50 and 0.75 quantiles.

For PHN presenters the relationship was similar to hospital presenters with a linear relationship between 'field FMC-CCL' time and 'CCL-reperfusion' time, see Figure 7 The smoothed curve defined with three internal knots shows again a gradual increase in 'field FMC-CCL' time as CCL-reperfusion time increases i.e. from 20-67 minutes 'CCL-reperfusion' time increases from 24-33 minutes where the slope remains relatively constant to 34 minutes where the maximum 'Field FMC-CCL' time analysed of 89 minutes is reached.

***Figure 7**: Relationship between time points for Part Two (PHN)* *.*



* Using natural cubic smoothing splines with three knots at 0.25, 0.50 and 0.75 quantiles.

Figures 8 and 9 display the ≤90-minute target achievement threshold for 'FMC-reperfusion' time for hospital presenters and PHN presenters respectively. The percentage of patients meeting target parameters was similar.

Figure 8**:** *Achievement threshold of target ≤90 minutes for Part Two (Hospital).*

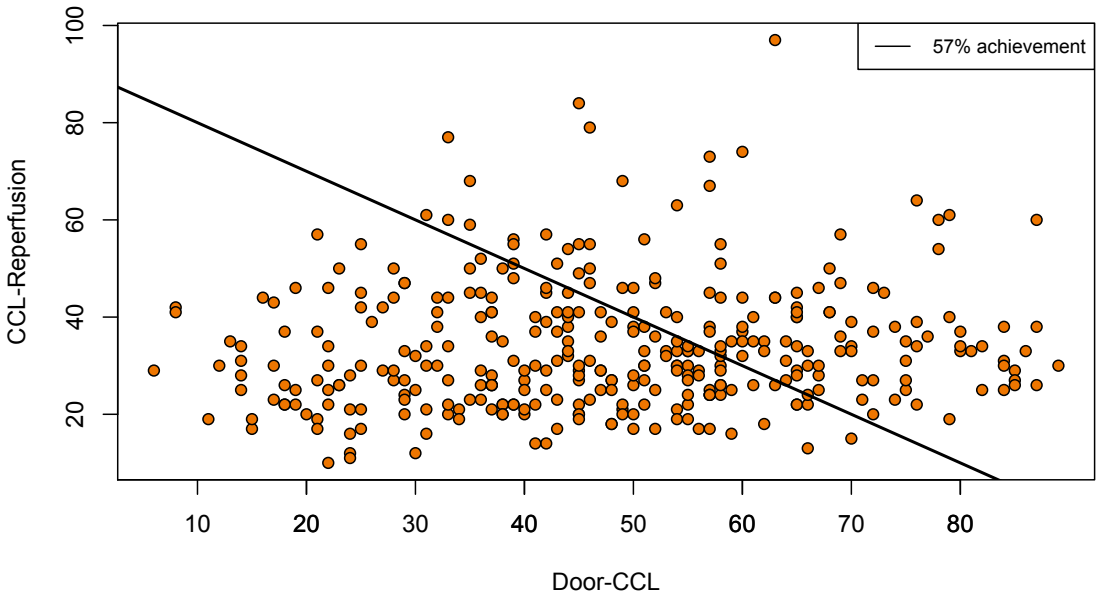
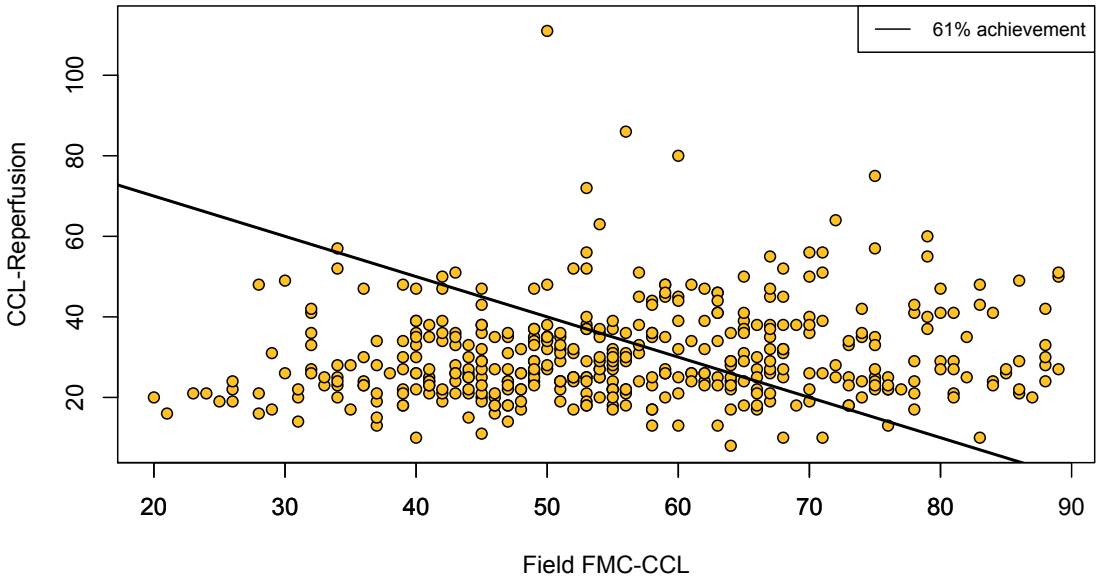


Figure 9**:** *Achievement threshold of target ≤90 minutes for Part Two (PHN).*



The predicted probability of achieving the reperfusion performance targets versus 'FMC-CCL' time according to mode of presentation is plotted in Figures 10 and 11 The figures identify the calculated points of interest or 'third derivative'. Each plot displays the 50% probability point for 'FMC-CCL' time used to create a delineation point in the interval groups formed in the proceeding quantile regression analysis.

Figure 10 displays the predicted probability of hospital presenters achieving the reperfusion target of ≤90 minutes versus 'Door-CCL' in minutes. The was a gradual linear decline until 66 minutes at which point the decline visibly slows down. There are four points of interest where the shape of the probability curve visibly changes. At 29 minutes there is a point of interest where the probability is 97% (95% CI 91-100%); at 37 minutes the probability is 86% (95% CI 76-95%); at 56 minutes the probability is 65% (95% CI 54-76%); and finally at 66 minutes the probability is 14% (95% CI 5-24%). The 50% probability was calculated at 59 minutes. For every one-minute increase in 'Door-CCL' time between 0-66 minutes there is an estimated decreased probability of 0.1%, on average, in achieving the reperfusion target.

Figure 10: *Probability of achieving reperfusion ≤90 minutes for Part Two (Hospital).*

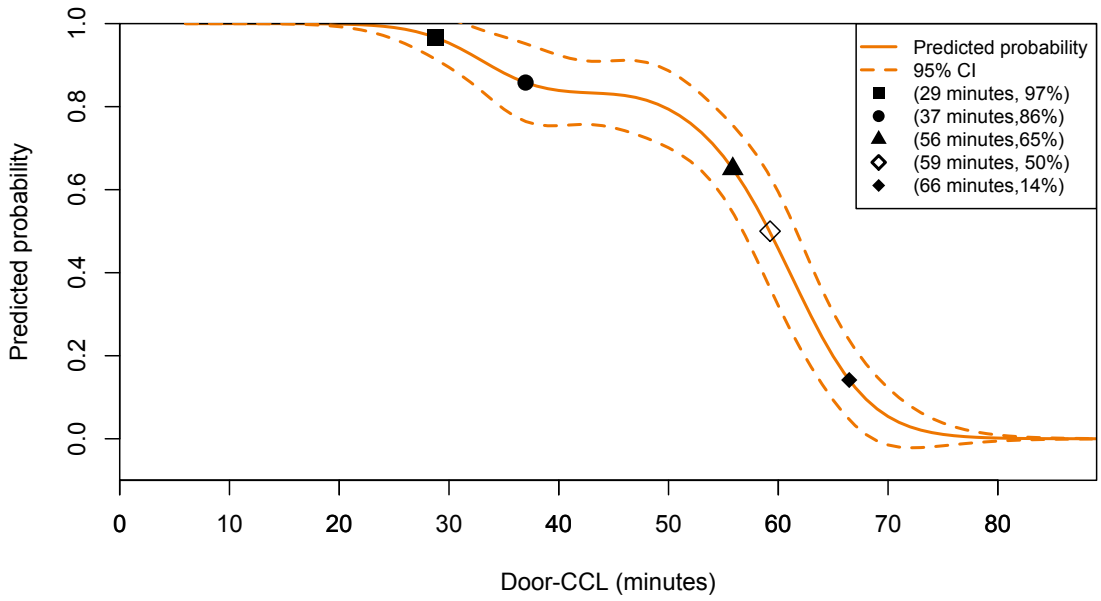
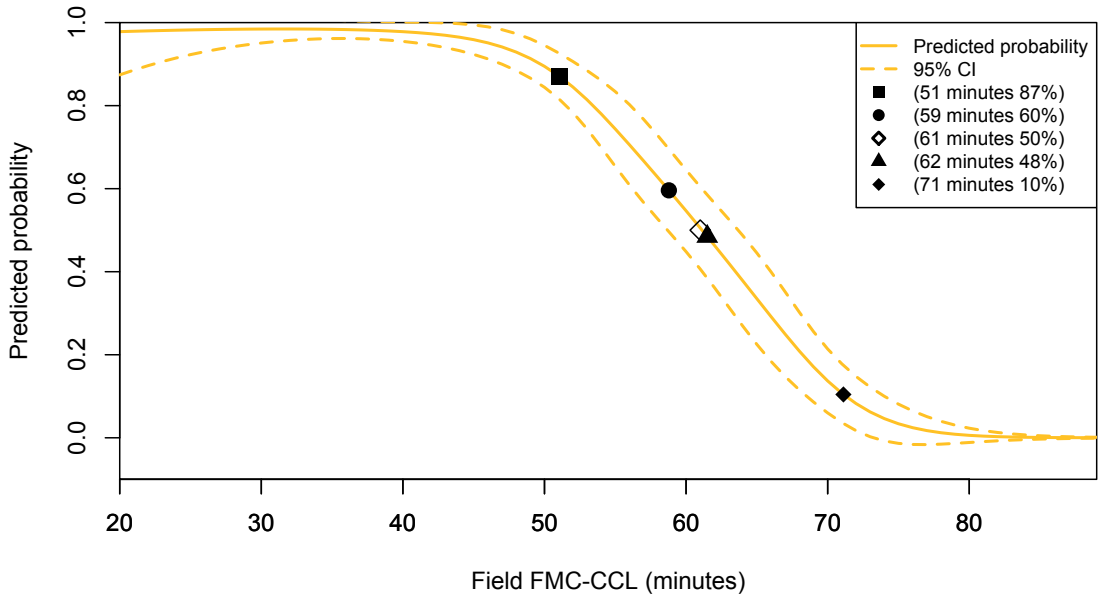


Figure 11 displays the predicted probability of PHN presenters achieving the reperfusion target of ≤90 minutes versus 'Field FMC-CCL' in minutes. There was a slow then gradual linear decline until 71 minutes at which point the decline visibly slows down. There are again four points of interest where the shape of the probability curve visibly changes. At

51 minutes there is a point of interest where the probability is 87% (95% CI 81-93%); at 59 minutes the probability declines to 60% (95% CI 49-70%); at 62 minutes the probability is 48% (95% CI 38-58%); and finally at 71 minutes the probability is 10% (95% CI 3-17%). The 50% probability was calculated at 61 minutes. For every one-minute increase in 'Field FMC-CCL' between 0-71 minutes there is an estimated decreased probability of 0.2%, on average, in achieving the reperfusion target.

Figure 11: *Probability of achieving reperfusion ≤90 minutes for Part Two (PHN).*



Figures 12 and 13 display the results of the quantile regression addressing the third research question; to identify predictors of 'CCL-reperfusion' time in minutes.

The quantile regression analysis for hospital presenters is shown in Figure 12. Controlling for all other variables there were no statistically significant predictors associated with prolonged CCL-reperfusion time. Presentation out of business hours was the only covariate trending to statistical significance, with an estimated increase in 'CCL-reperfusion' time by 5 minutes (95% CI 0-8 minutes) when compared to patients presenting during business hours.

***Figure 12**: Quantile Regression for Part Two (Hospital).*

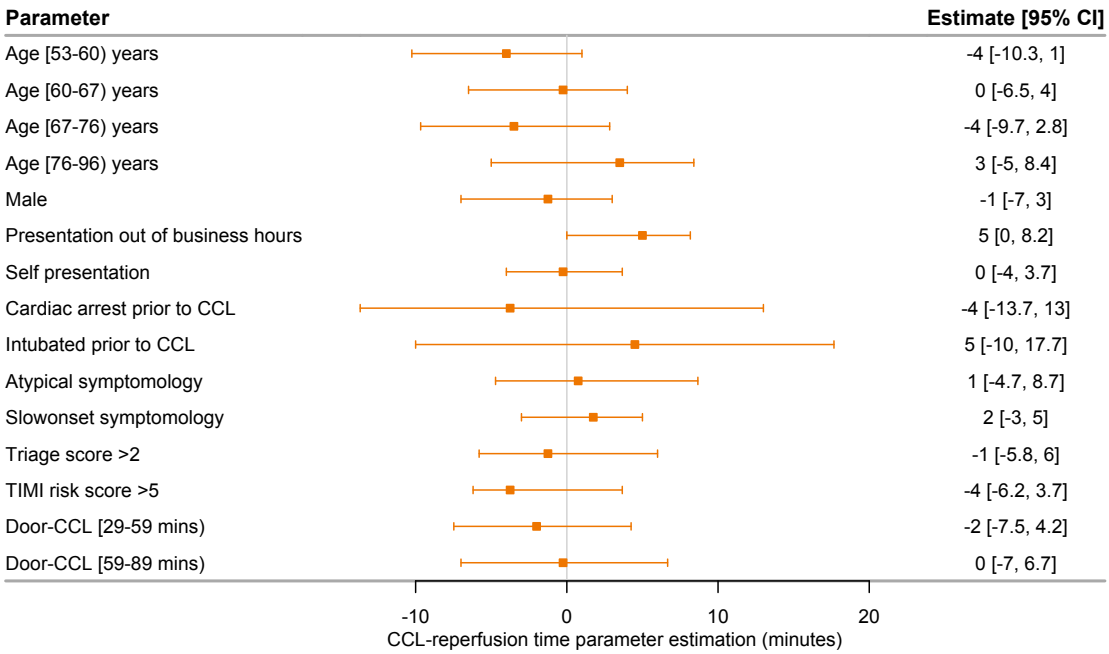
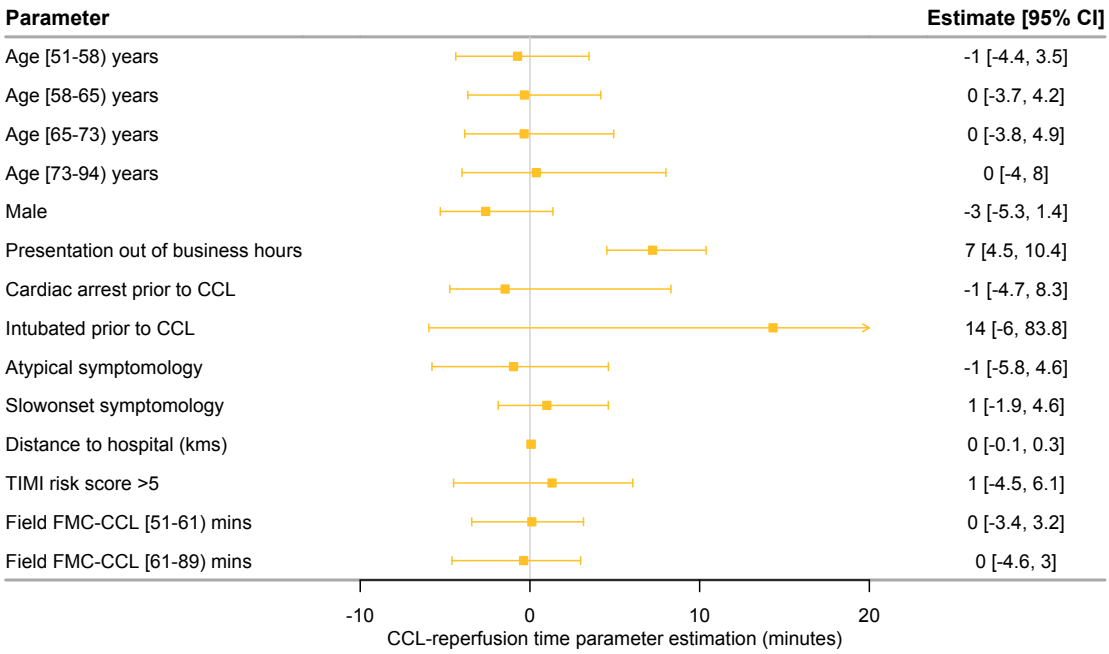


Figure 13 displays the quantile regression analysis for PHN presenters, finding one statistically significant independent predictor. Patients presenting out of business hours had an estimated median increase in 'CCL-reperfusion' time by 7 minutes (95% CI 5-10 minutes) compared to patients presenting during business hours.

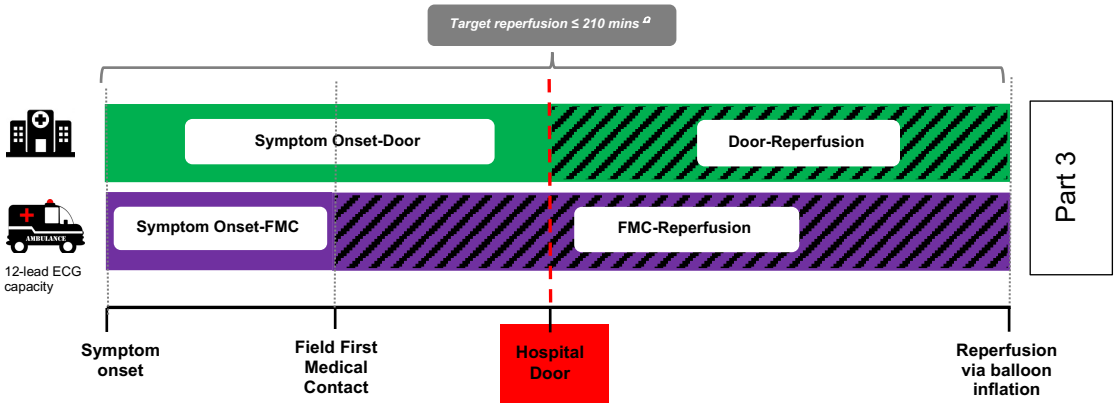
***Figure 13**: Quantile Regression for Part Two (PHN).*



5.3 Study II Part Three: Time to FMC and reperfusion targets.

The following presents the results of Part Three which examines the final two parameters of interest: the time taken for STEMI patients from symptom onset to reach FMC (in the field or hospital); and the time taken for reperfusion to subsequently take place. Figure 14 illustrates the exact time points measured for each subset i.e. 'hospital presenters' or 'PHN presenters' and defines the reperfusion target.

Figure 14: *Overview of time points analysed for (Study II Part Three).*



Ω ACCF/AHA guidelines for all STEMI patients.

Table 5 displays the univariate analysis of baseline clinical characteristics and outcomes for the time parameter of 'symptom to reperfusion' for hospital and PHN presenters. Statistically significant differences were found. Hospital presenters had a higher percentage of atypical symptoms than PHN presenters, 16% vs 7% ($p<0.01$). Hospital presenters took longer to seek medical contact than PHN presenters with 'symptom onset-FMC time' 89 vs 49 minutes ($p<0.001$), respectively. Mortality rates in hospital and at 12 months were higher for hospital presenters than PHN presenters 12% vs 4% ($p<0.001$); and 14% vs 5% ($p<0.001$) respectively. Interestingly, given the above results PHN presenters were more likely to have an abnormal LV ejection fraction than hospital presenters, 16% vs 7% ($p<0.01$).

Table 5: *Characteristics of Part Three (n=628)*

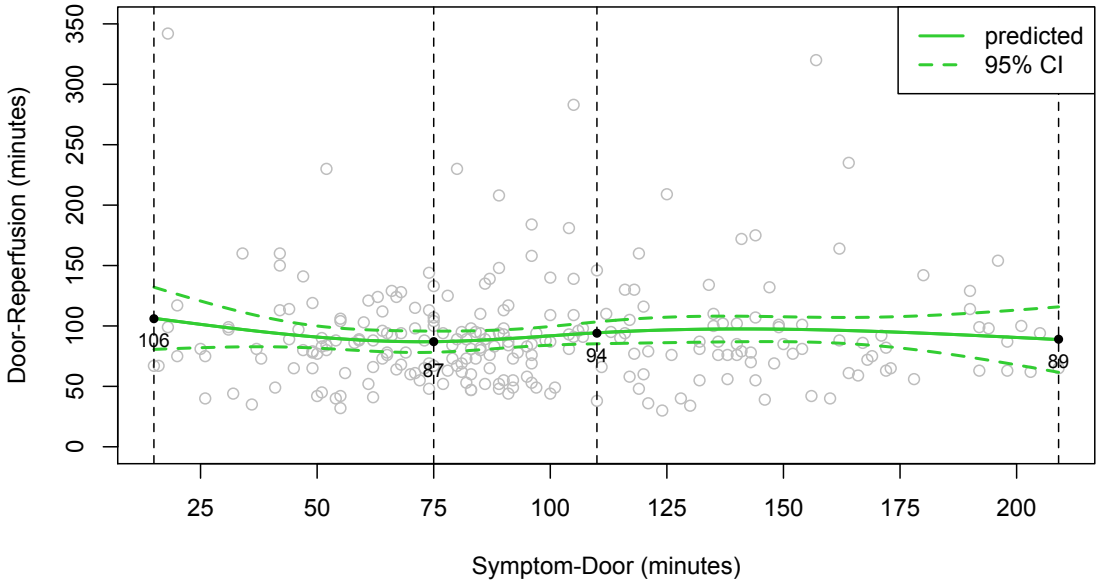
	Hospital presenters (n=244)	PHN presenters (n=384)
Age *mean ± SD (years)*	64 ± 13	62 ± 13
Female *n (%)*	52 (21%)	64 (16%)
Presentation in business hours *(0800-1800hrs Mon-Fri)*	90 (37%)	128 (33%)
Mode of presentation to hospital		
Self-presentation *n (%)*	75 (31%)	x
Regular Ambulance presentation *n (%)*	169 (69%)	x
Pre-Hospital Notification (PHN) n (%)	x	384 (100%)
Distance to Hospital (PHN only) median *(Q1-Q3) (km)*	x	10 ± 6
Atypical symptomology Ω *n (%)*	**36 (16%)**	**26 (7%) ****
Slow onset symptomology † *n (%)*	48 (21%)	78 (21%)
Assigned Triage score > 2 (Hospital only #**)** *n (%)*	24 (10%)	x
Cardiac arrest prior to CCL arrival *n (%)*	31 (13%)	45 (12%)
Intubated prior to CCL arrival *n (%)*	27 (11%)	26 (7%)
TIMI risk >5 *n (%)*	65 (27%)	73(19%)
Outcomes		
Achievement threshold of Reperfusion time ≤ 210 minutes n (%)	182 (75%)	325 (81%)
'Symptom onset' - 'Door' or 'Field FMC' time *median minutes (IQR)*	**89 (66-127)**	**49 (30-87) *****
'Door' or 'Field FMC' - 'Reperfusion' time *median minutes (IQR)*	85 (65-104)	88 (74-108)
Abnormal Left Ventricular Ejection Fraction *n (%)*	**29 (17%)**	**77 (28%) ****
Length of Stay *median (Q1-Q3) days*	4.0 (3-5)	3.5 (3-4)
In-hospital mortality *n (%)*	**30 (12%)**	**16 (4%) *****
365-day mortality *n (%)*	**34 (14%)**	**18 (5%) *****

Ω Back pain, fatigue, GI distress, palpitations, dizziness/faintness; † any typical or atypical pain that is gradual or intermittent in nature.

all PHN patients were allocated a triage score of 1on admission. Statistically significant *p<0.05; **p<0.01; ***p<0.001

The relationship between 'Symptom-Door' time and 'Door-Reperfusion' time for hospital presenters was non-linear and is shown in Figure 15. The smoothed curve defined with two internal knots demonstrates a combination of gradual upward and downward changes to the slope as 'Symptom-Door time increases. Between 15-75 minutes 'Door to reperfusion' time declines from 106-87 minutes, at which point this time parameter increases to 94 minutes over the next 30 minutes. After which between 105-209 minutes 'Door-reperfusion' gradually declines to 89 minutes.

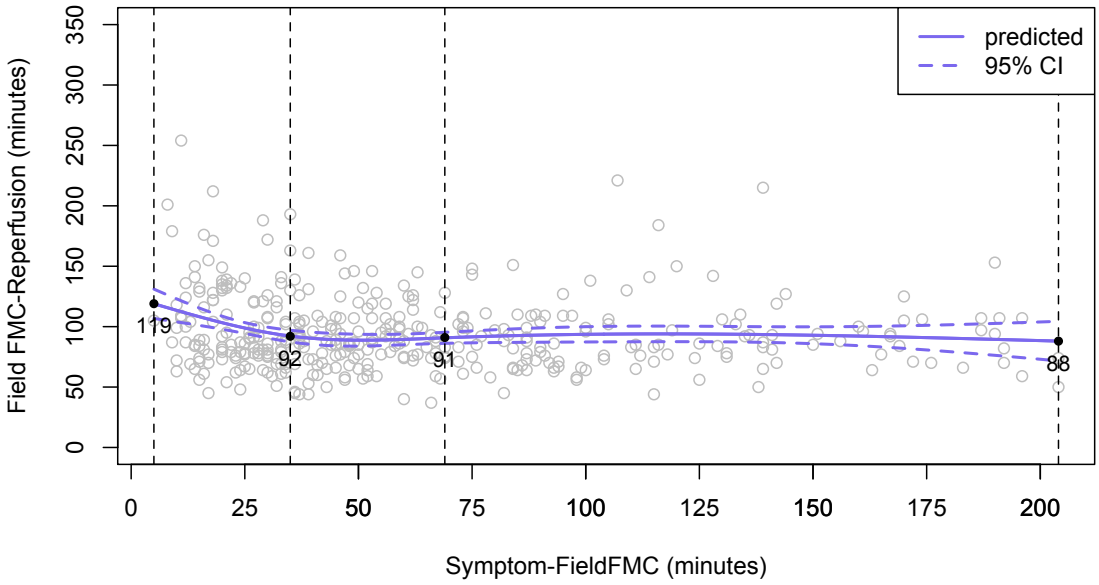
Figure 15: *Relationship between time points for Part Three (Hospital).*



* Using natural cubic smoothing splines with two knots (at 0.33 and 0.66 quantiles).

For PHN presenters the relationship between 'Symptom-Field FMC' time and 'Field FMC-reperfusion was interestingly different to hospital presenters and is shown in Figure 16. The smoothed curve defined with two internal knots demonstrates a gradual linear decline in 'Field FMC-Reperfusion' time as 'Symptom-Field FMC' time increased. From 5-35 minutes the 'Field FMC-Reperfusion' time decreases from 119-92 minutes, where the slope remains relatively constant at 91-88 minutes until the maximum 'Symptom-Field FMC' time analysed is reached.

***Figure 16**: Relationship between time points for Part Three (PHN).*



* Using natural cubic smoothing splines with two knots (at 0.33 and 0.67 quantiles).

Figures 17 and 18 illustrates the ≤210-minute target achievement threshold for 'symptom-reperfusion' time for hospital presenters and PHN presenters respectively. There was a numerical difference with 75% of hospital presenters versus 81% of PHN patients achieving the target threshold.

***Figure 17**: Achievement threshold of target ≤210 minutes for Part Three (Hospital).*

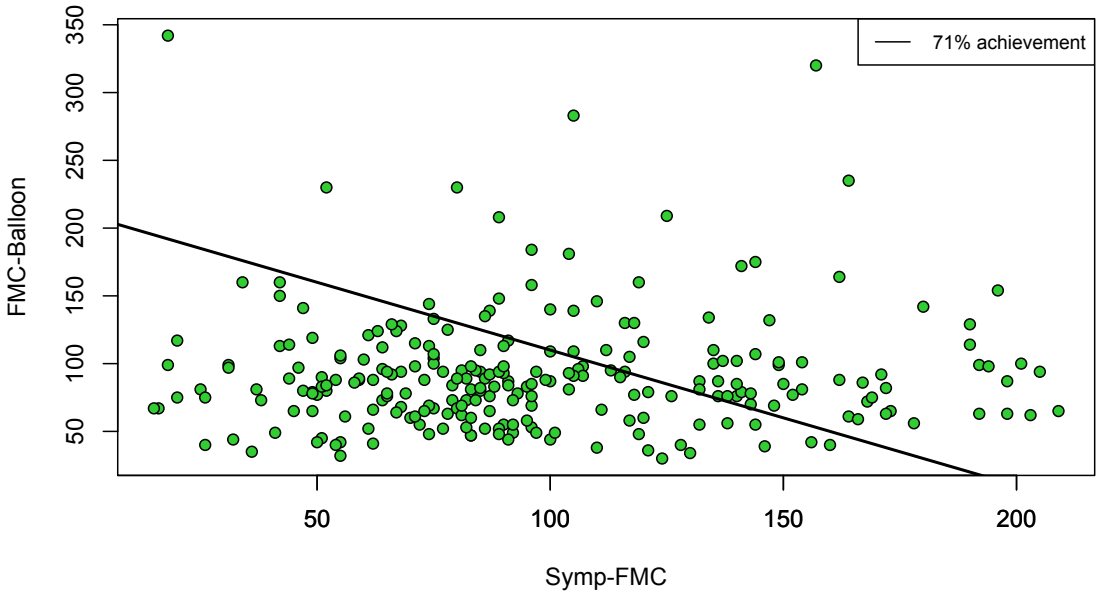
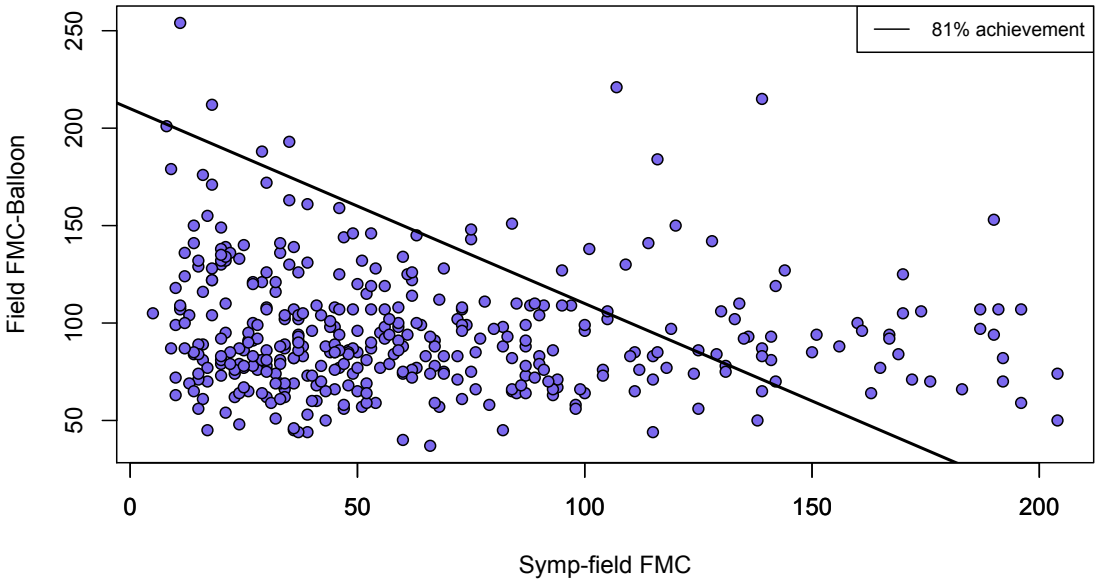


***Figure 18**: Achievement threshold of target ≤210 minutes for Part Three (PHN).*



The predicted probability of achieving the reperfusion performance targets versus 'Symptom-FMC' time according to mode of presentation is plotted in Figures 19 and 20. The figures identify the calculated points of interest or 'third derivative'. As described in aforementioned Part Two, each plot displays the 50% probability point for 'Symptom-FMC' time used to create the delineation point for the interval groups used in the proceeding quantile regression analysis.

Figure 19 displays the predicted probability of hospital presenters achieving the total ischaemic time target of ≤210 minutes versus 'Symptom-Door' in minutes. The probability curve shows an initial increase then a linear decline from 42 minutes until 136 minutes at which point the decline visibly slows down. There are two points of interest where the shape of the probability curve visibly changes. At 99 minutes there is a point of interest where the probability is 81% (95% CI 73-89%) and at 136 minutes the probability is 26% (95% CI 14-38%). The 50% probability was calculated at 119 minutes. For every one-minute increase in 'Symptom-Door' time between 42-136 minutes there is an estimated decreased probability of 0.1%, on average, in achieving the reperfusion target.

***Figure 19**: Probability of reperfusion target ≤210 minutes for Part Three (Hospital).*

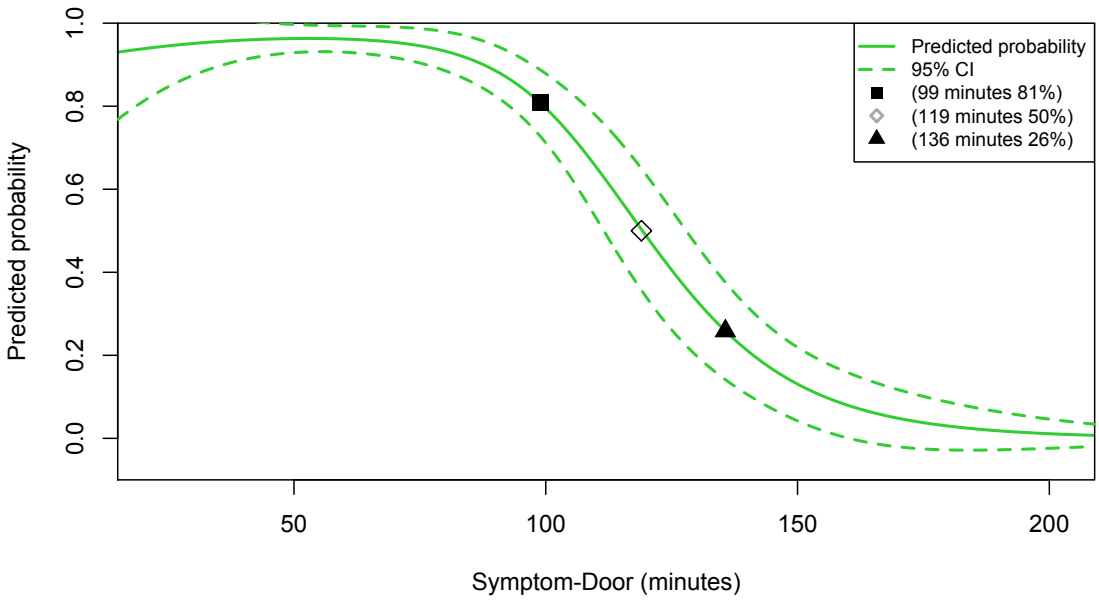
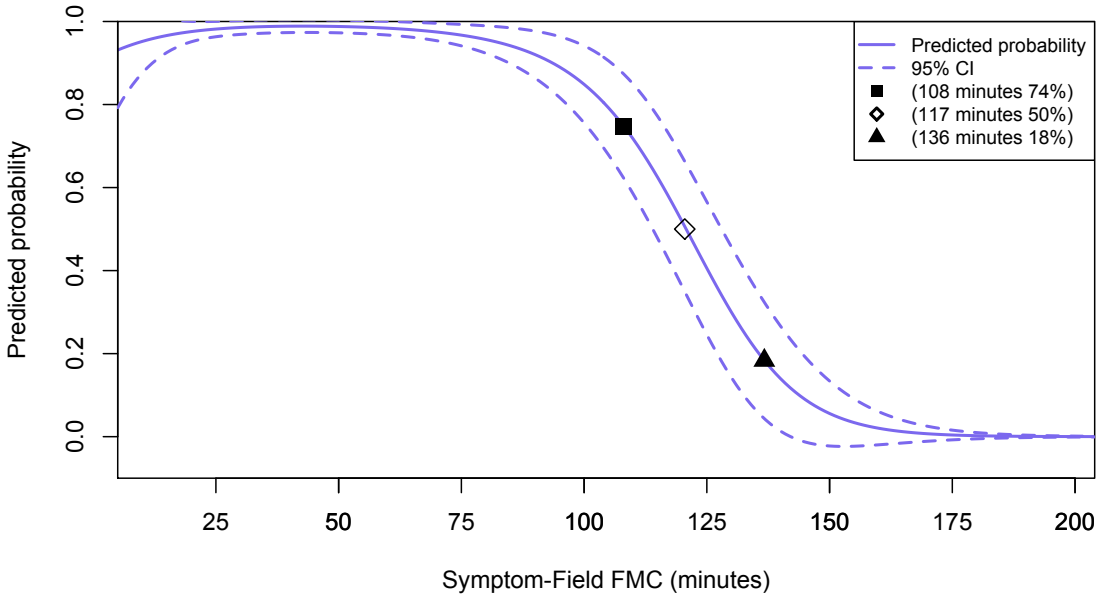


Figure 20 displays the predicted probability of PHN presenters achieving the total ischaemic time target of ≤210 minutes versus 'Symptom-Field FMC' in minutes. Similarly, to the previous Figure 5.15, the probability curve shows an initial increase then a linear decline from 46 minutes until 136 minutes at which point the decline visibly slows down. There are two points of interest where the shape of the probability curve visibly changes. At 108 minutes there is a point of interest where the probability is 74% (95% CI 62-87%) and at 136 minutes the probability is 18% (95% CI 4-32%). The 50% probability was calculated at 117 minutes. For every one-minute increase in 'Symptom-Field FMC' time between 46-136 minutes there is an estimated decreased probability of 0.1%, on average, in achieving the reperfusion target.

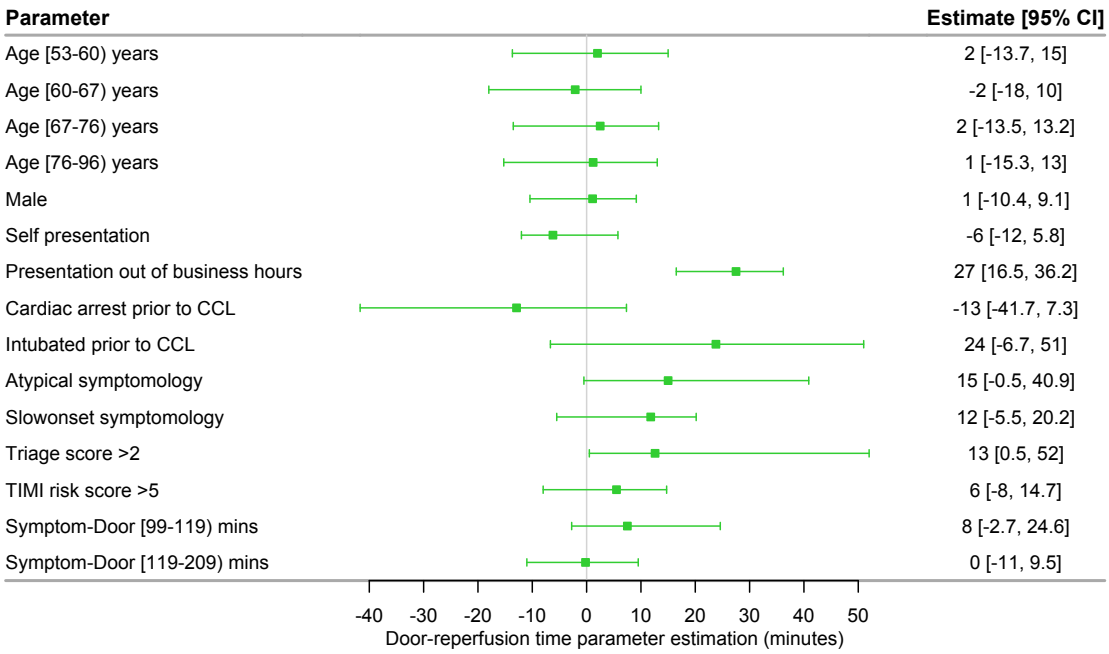
***Figure 20**: Probability of reperfusion target ≤210 minutes for Part Three (PHN).*



Figures 21 and 22 display the results of the quantile regression addressing the third research question; to identify predictors of 'FMC-reperfusion' time in minutes.

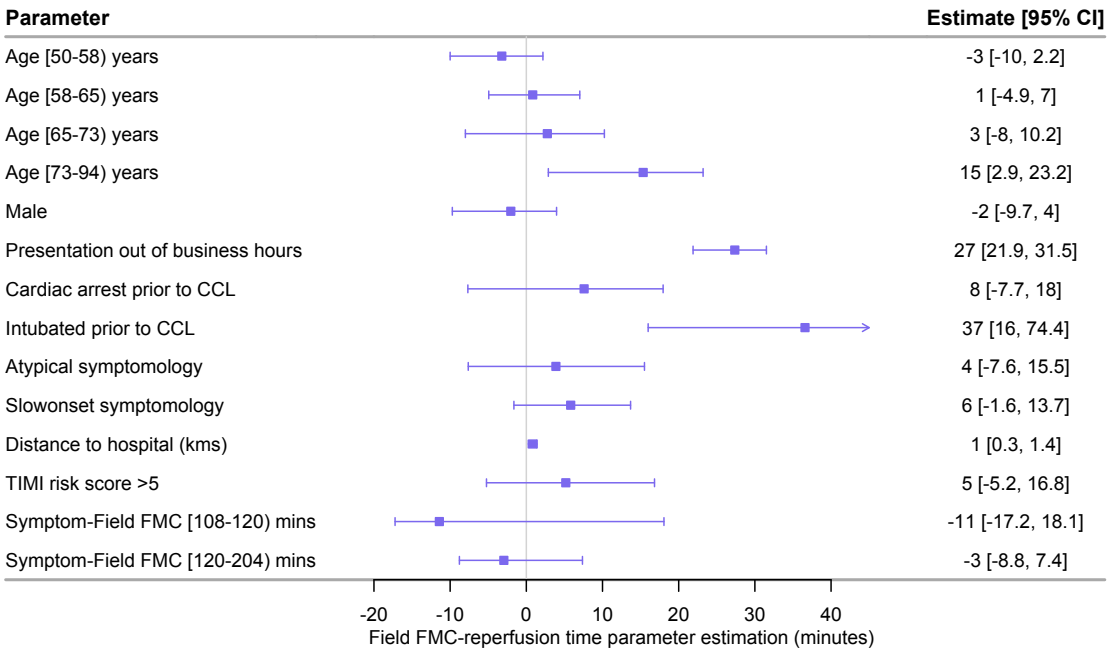
The quantile regression analysis for hospital presenters is shown in Figure 21. Controlling for all other variables presentation out of business hours was the only statistically significant predictor associated with prolonged 'Door-reperfusion' time. An estimated increase in 'Door-reperfusion' time by 27 minutes (95% CI 17-36 minutes) was calculated for patients presenting out of hours when compared to patients presenting during business hours.

Figure 21: *Quantile Regression for Part Three (Hospital).*



The quantile regression analysis for PHN presenters is shown in Figure 22. When controlling for all other variables there were four statistically significant predictors associated with prolonged 'field FMC-reperfusion' time. There was an estimated increase in the median 'field FMC-reperfusion' time for the following factors: older age between 74-95 years (when compared with the <51 year age group) by 15 minutes (95% CI 3-23 minutes); presenting out of business hours (when compared to in business hours) by 27 minutes (95% CI 22-32 minutes); being intubated prior to CCL (when compared to those who were not) by 37 minutes (95% CI 16-74 minutes); and finally distance to the destination hospital, by an estimated 1 minute for every 1km to hospital (95% CI 0.3-1.4).

Figure 22: *Quantile Regression for Part Three (PHN).*



5.4 Chapter summary

This chapter has reported the results of the timepoint analysis from a single centre tertiary STEMI database. Three sets of timeframes were analysed using two separate subsets that grouped data depending on mode of presentation. As defined in Chapter One, 'Hospital presenters' were any patient who self-presented to hospital or arrived via regular ambulance (with no PHN). 'PHN presenters' were defined as any patient who had a confirmed STEMI diagnosis and activation of cardiac catheterisation laboratory (CCL) services prior to hospital arrival.

In Part One, the results of the first set of research questions for Study II were reported. There was a linear relationship found between 'FMC-ECG' time and 'ECG-reperfusion' time for both subsets. The shortest 'FMC-ECG' time associated with the highest probability of achieving the 90-minute performance target for each subset was ≤7 minutes for hospital presenters and ≤6 minutes for PHN presenters. Quantile regression found time to ECG >7 minutes, and presentation out of business hours was associated with prolonged 'ECG-reperfusion' time for hospital presenters. For PHN presenters, quantile regression demonstrated independent predictors associated with both prolonged and reduced 'ECG-reperfusion' time. Out of business hour presentation, intubation prior to CCL, age ≥75 years and distance to destination hospital were associated with prolonged 'ECG-reperfusion' time. A field 'FMC-ECG' time between 19-67 minutes and male gender were associated with a reduction in 'ECG-reperfusion' time.

In Part Two, the results for the second set of research questions for Study II were reported. The relationship between 'FMC-CCL arrival' time and 'CCL-reperfusion' time for both subsets was linear. The shortest 'FMC-CCL arrival' time associated with the highest probability of achieving the 90-minute performance target for each subset was ≤29 minutes for hospital presenters and ≤51 minutes for PHN presenters. Quantile regression demonstrated 'FMC-CCL' had no independent effect on 'CCL-reperfusion' time for both subsets, however presentation out of business hours was independently associated with prolonged 'CCL-reperfusion' time for both subsets.

In Part Three, the results of the third set of research questions were reported. The relationship between 'Symptom onset-FMC' time and 'FMC-reperfusion' time identified a non-linear relationship for hospital presenters, and a linear relationship for PHN presenters. The shortest 'Symptom onset-FMC' time associated with the highest probability of achieving the 210-minute performance target for each subset was ≤99

minutes for hospital presenters and ≤108 minutes for PHN presenters. Quantile regression found ‘Symptom onset-FMC’ time had no independent effect on ‘FMC-reperfusion’ time for both subsets. For hospital presenters, quantile regression demonstrated presenting during out of business hours to be independently associated with a prolonged ‘FMC-reperfusion’ time. For PHN presenters, presenting out of business hours, older age, being intubated prior to CCL arrival and distance to destination hospital were found to be independently associated with a prolonged ‘FMC-reperfusion’ time.

The next chapter will present the results for Study III.

CHAPTER 6: RESULTS FOR STUDY III

6.1 Chapter introduction

The following chapter reports the results of Study III, the frontline clinician FLUME survey. The publication of the FLUME study is included in this chapter. The FLUME survey addressed the third aim for this thesis, that is, to explore the perceived barriers to effective STEMI management as reported by frontline clinicians. The three research questions addressed by the study were: What are the most commonly occurring barriers to timely STEMI management for paramedics and emergency nurses? Are there differences in barriers experienced by paramedics and emergency nurses? Are there differences in barriers experienced by frontline clinicians in rural and metropolitan settings?

6.2 Study III (Accepted Publication)

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Research paper

Frontline barriers to effective paramedic and emergency nursing STEMI management: clinician perspectives

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ABSTRACT

Background: Factors that hinder the pivotal role frontline clinicians play in STEMI management are under-reported. We aimed to explore perceived barriers to effective STEMI management by addressing the following questions:

1. What are the most commonly occurring barriers to timely STEMI management for paramedics and emergency nurses?
2. Are there differences in barriers experienced by paramedics and emergency nurses?
3. Are there differences in barriers experienced by frontline clinicians in rural and metropolitan settings?

Methods: A 79-item online survey was offered to paramedics and emergency nurses. Descriptive statistics and exploratory factor analysis identified the most frequently experienced types of barriers. Professional groups and geographical locations were compared.

Results: There were 333 respondents. Response rates for paramedics was 10% and 9% for members of an emergency nursing association. Most commonly occurring barriers across all respondents were: 'lack of skills development'; 'lack of feedback'; 'untimely support'; 'distance to scene/hospital facilities'; 'hospital-related delays'. Statistically significant differences were found by professional group and geographical location.

Conclusion: Barriers to timely management were present, but not frequently experienced. Survey responses indicate a need for improved continuing professional development opportunity, clearer feedback mechanisms, streamlined facilitation of STEMI processes in hospitals, and enhanced access to expert advice/resources for all frontline clinicians.

Introduction

ST elevation myocardial infarction (STEMI) management is a time sensitive and multidisciplinary process of care, that requires collaboration across organizational boundaries, including Emergency Medical Services (EMS), Hospital Emergency Room Staff, Interventional Cardiology teams and coronary care units. Guidelines recommend parameters for 'time to diagnosis' and 'time to reperfusion' in STEMI management [1]. Frontline clinicians play a pivotal role in achieving these performance targets. The initial contact with a presumed STEMI patient demands an abbreviated medical encounter to elicit and assess, often with limited access to the patient's medical history. The ensuing trajectory of care entrusts a frontline clinicians' expertise to diagnose STEMI from a 12-lead ECG and initiate the expedited process of care to restore coronary blood flow.

There is literature examining the influence that 'patient' and 'non-patient factors' have on the delivery of timely STEMI management. Patient related factors such as advanced age, female gender, low socioeconomic status, symptomatology, poor health literacy and living alone/being alone at symptom onset are reported as delays in seeking medical treatment [2,3]. Little has improved over the decades in relation to patient related delay [4], despite clinical

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trials to improve health seeking behaviours [5]. However, recent Australian mass media campaigns designed to raise patient awareness of signs and symptoms appear to have had a positive impact [6].

Non-patient factors, such as systems of care and organisational culture, also affect the ability for organisations to deliver timely STEMI management. Past literature indicates robust systems of care that incorporate facilitated rapid response strategies to STEMI and provide timely clinical performance feedback are determinants of achieving targets in STEMI management [7].These strategies are recommended at the national level [8]. In contrast, there is evidence that demonstrates non-patient factors contribute to delayed STEMI management, such as out of business hour presentations [9], overcrowding in emergency departments (ED) [10], mis-dispatch of paramedic services [11] and under-triaging in EDs [12].

For frontline clinicians there is an evident intersection of some 'non-patient factors' and 'patient factors', that require rapid navigation and response. For example, dispatch of paramedic services and ED triaging of patients have an interdependency on the information patients communicate to the frontline clinician. Poor health literacy levels, atypical symptomatology and pre-existing comorbid conditions may contribute to delay in these processes.

There is limited literature reporting barriers that may impact a frontline clinicians' ability to contribute to this expedited process of care. Kayipmaz et al. surveyed 225 emergency medicine specialists, exploring STEMI management practices across Turkey. They reported compliance with guidelines rather than identifying barriers to STEMI management practices [13]. A Canadian qualitative study by Rajabali et al. explored the perceived barriers and facilitators contributing to delivery of pre-hospital thrombolysis. They found variation in the implementation of 'processes and protocols' along with how staff perceived ownership of and responsibility for the STEMI patient [14]. Magid et al., surveyed 3562 ED physicians with the broad aim of assessing design, management and support of EDs. They concluded investment in physical design, increasing human resources during periods of high demand, and reworking processes of care to improve the flow of information and patients were required [15].

To our knowledge there is no known literature exploring the challenges for frontline clinicians in Australia. The primary objective of this study is to identify the most common barriers experienced by frontline clinicians, specifically paramedics and emergency nurses, in the delivery of STEMI management across the state of Victoria, Australia. A secondary objective is to compare results by professional group and geographical location.

The following research questions will be addressed:

1 What are the most commonly occurring barriers to timely STEMI management for paramedics and emergency nurses?
2 Are there differences in barriers experienced by paramedics and emergency nurses?
3 Are there differences in barriers experienced by frontline clinicians in rural and metropolitan settings?

Methods

Setting

This study targeted the Australian state of Victoria. The population of Victoria is 6.32 million and approximately 4 million live in metropolitan Melbourne [16]. There are 40 public hospitals with EDs in Victoria; 23 located in metropolitan and 17 in regional/rural areas [17].

STEMI reperfusion strategies in Victoria vary by geographical location and mode of presentation. All large metropolitan tertiary level hospitals routinely provide a 24/7 primary percutaneous coronary intervention (PCI) service. Ambulance presentations who fulfil STEMI 12-lead ECG criteria in the field utlise a pre-hospital notification (PHN) system. The responding paramedics alert the destination hospital by transmiting the ECG which activates cardiac catheter laboratory (Cath Lab) services prior to hospital arrival. Up until mid-2017 this PHN system was restricted to mobile intensive care ambulance (MICA) paramedics, however since this time advanced life support (ALS) paramedics have been trained and equipped to acquire and transmit ECGs to all metropolitan hospitals.

In contrast, some Victorian regional hospitals utilise the same PHN system described above for STEMI patients, if Cath Lab services are available, otherwise both regional and rural areas administer pharmacoinvasive therapy or 'thrombolysis 'as the STEMI reperfusion strategy. Since March 2015, MICA paramedics have had the capacity to administer pre-hopsital thrombolysis (PHT). However, these established regional/rural STEMI systems were in a state of flux at the time of survey. Under the auspices of the Victorian ambulance service, all regional/rural ALS paramedics were in the process of being trained and equipped to administer PHT which was completed by March 2018. This process was also supported by a Cardiology consult hotline that was operational from April 2017. Additionally, one regional area of Victoria was trialling an app-based communication tool for STEMI and stroke management to improve timely processes of care.

Participants

Two organizations were approached to participate in this stakeholder survey. The first, Ambulance Victoria (AV), the sole organization that employs all 3450 operational paramedics in Victoria; 520 Mobile Intensive Care Ambulance (MICA) paramedics and 2930 Advanced Life Support (ALS) paramedics. The known geographical location of operational paramedics offered by the 'People and Culture Division' of AV is 59% metropolitan and 41% regional/rural operational employees. The second, the College of Emergency Nursing Australasia (CENA); a professional organization representing emergency nurses across Australia. Since the target state was Victoria, survey distribution was restricted to the organization of AV and the 452 financial Victorian members of CENA. Recruitment via CENA was chosen because of the difficulties in accessing the total target population of triage nurses in Victoria. The required ethical approval process to achieve this would have exceeded the authors' time restraints to conduct this study.

Research ethics statement

Our survey conformed to the relevant ethical guidelines. The study was granted approval from La Trobe University, AV and CENA (Victorian Branch). The approval numbers were S17-011; R17-003 and CENA/RC/2017/03 respectively.

Procedure

An 79-item online survey was generated using Qualtrics©. An email invitation was distributed, via the industry stakeholders, with a participant information statement (PIS) and electronic link to the Qualtrics© platform. Commencing the survey was deemed to indicate consent. Recruitment strategies included posters and use of social media. An incentive of a $250 VISA debit card prize draw was employed to maximize response rates. The survey data collection period was over a five month period, between the dates 1-August 2017 to 15-December 2017.

Survey development

The survey was developed by the research team of experienced cardiac nurses, health service evaluators, health science researchers and interventional cardiologists. Two of these team

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Table 1
Demographics of Cohort.

	Total (n = 333)	Paramedics (n = 293)	Emergency Nurses (n = 40)
Years' experience *(mean ± SD)*	13 ± 9	13 ± 10	12 ± 8
Number of presumed STEMI patients treated/week *(mean ± SD)*	2.5 ± 0.7	2.6 ± 0.6	1.7 ± 0.8
Dual Qualifications (i.e paramedicine and nursing) *n (%)*	73 (22%)	68 (23%)	5 (13%)
Metropolitan practitioner *n (%)*	124 (37%)	101 (34%)	23 (58%)
Regional/Rural practitioner *n (%)*	209 (63%)	192 (66%)	17 (42%)

members had extensive experience in survey methodology, administration and analysis. Survey design combined clinical experience, known literature of the barriers to timely STEMI management, and utilisation of the Theoretical Domains Framework (TDF). The TDF is an integrated model that draws on psychological theory relevant to the implementation of evidence based practice, and simplifies these theories by categorizing them into key behaviour change domains [18,19]. The use of TDF and its validity in process evaluation has been reported [20,21]. For this study the TDF was used only as a sensitising tool to comprehensively represent possible barriers to timely STEMI management.

Cognitive testing to establish the content validity [22] occurred with a convenience sample of 12 experienced paramedics and Emergency nurses. Minor modifications were made based on this feedback, with item retention, modification and deletion ensuring alignment with the study aims [23].

The survey has five distinct sections: 1) presence of workplace policies and procedures; 2) respondent's commitment to guidelines (expressed as proportion of the time guidelines are achievable); 3) proportion of time organizational/environmental characteristics affect timely management of STEMI; 4) points of communication affecting timely management of STEMI; 5) respondent's levels of confidence to recognise and response to suspected STEMI. The first survey set provided the response options "Yes',' No', 'NA' (not applicable) or 'Don't know'. The other four survey sections utilised a visual analogue scale (VAS) with a rating labelled at each end: "0–100% of the time" for sections 2, 3 and 4; and "0–100% confident" for section 5. All VAS questions were worded containing one concept to provide a consistent unipolar interpretation of responses. In addition, opened ended questions were offered allowing respondents to elaborate on their answers and/or raise issues not identified in the survey (see Table A1 for the survey tool).

Statistical analysis

Descriptive analyses were undertaken for demographic questions and section one of the survey. Exploratory factor analysis was undertaken on sections two to five to explore whether the individual items grouped into types of barriers. The purpose of the factor analysis was to simplify reporting and to enable comparisons between different groups of respondents with fewer repeated tests of significance [24]. Solutions that provided the most coherent factors with the least duplication of item loadings when analysing sections of the survey items were selected using either principal component analysis (PCA) or principal axis factoring (PAF). The final composition and labelling of the types of barriers were agreed by the research team. Comparison of responses to the types of barriers by professional group and geographical location was undertaken using either parametric or non-parametric testing according to the data distribution. IBM SPSS Statistics for Mac, Version 24 (IBM Corp., Armonk, N.Y., USA) was used for this statistical analysis. Analysis of the open ended questions was undertaken with similar content grouped and coded as themes in line with the approach recommended by Braun and Clarke [25]. The purpose of this analysis was to confirm that the representation of barriers included in the survey was comprehensive, and to identify any issues not captured.

Results

There were 333 responses to the survey: 293 paramedics and 40 emergency nurses, with broad representation across geographical locations in Victoria. The characteristics of the cohort are outlined in Table 1.

Commonly occurring barriers for all respondents

Fourteen barriers were identified, with 12 of these barriers derived through factor analysis. The other two represent two categories of policies and procedures; seven items were related to organisational and/or system governance and three were related to support for clinical skills of staff. The types of barriers most commonly experienced across all respondents were: 1) lack of clinical skills development; 2) lack of feedback; 3) untimely access to clinical support; 4) lack of confidence in symptom assessment; and 5) lack of confidence in unique ECG patterns. No new barriers or issues were identified in the responses to the open ended questions (see Tables A2 and A3).

Differences in barriers experienced by paramedics and Emergency nurses

Table 2 reports that four of the fourteen types of barriers were experienced statistically significantly more or less often by paramedics when compared to emergency nurses.

Differences in barriers experienced by clinicians in rural and metropolitan settings

Table 3 reports seven of the fourteen types of barriers were experienced statistically significantly more or less often by metropolitan clinicians when compared to rurally located clinicians.

Discussion

Our results demonstrate that Victorian paramedics and emergency nurses experienced similar barriers to timely STEMI management. Most barriers were not frequently experienced. The most common barrier type was lack of organisational and system governance, with 44% of respondents saying that their organisation lacked at least one standard policy or procedure that would support STEMI management. For the VAS frequency scale, barriers were at the lower end of the scale at 7–24%. Barriers experienced more frequently on the VAS scale were lack of clinical feedback (24%), untimely access to clinical support (20%), with lack of confidence in atypical symptom assessment, and unique ECG patterns (both at 19%).

There were statistically significant differences between professional groups for four of the fourteen barrier types. Emergency nurses reported a 'lack of organisational/system governance' more often than paramedics. This was further highlighted by the finding that paramedics reported higher frequencies of 'poor handover in the frontline environment' compared to Emergency nurses. These findings align with results from the Rajabali et al., study that concluded 'protocol and process' varied by professional groups

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Table 2
Perceived Quantitative Barriers compared by professional group.

Survey Section	Barrier Type after data reduction	All (n = 333)	Paramedics (n = 293)	Nurses (n = 40)	p value[c]
		Mean ± SD score of 'No' response[a]			
Workplace policies and procedures *10 survey items*	1. Lack of Organisational/System Governance *Survey items: 1, 3, 4, 5, 6, 7 & 10 (Reversed).*	0.12 ± 0.17 response rate n = 308 (93%)	0.11 ± 0.15 response rate n = 270 (92%)	0.20 ± 0.28 response rate n = 38 (95%)	0.04*
	2. Lack of clinical skills development *Survey items: 2, 8 & 9 (Reversed).*	0.44 ± 0.36 response rate n = 306 (92%)	0.44 ± 0.36 response rate n = 268 (91%)	0.40 ± 0.31 response rate n = 38 (95%)	0.54
		Median (IQR) of VAS[b] *score: 0–100% of the time*			
Commitment to guidelines *3 survey items*	3. Lack of belief in ACS guidelines *Survey items: 11, 12 & 13.*	10 (5–18) response rate n = 303 (91%)	10 (5–18) response rate n = 266 (91%)	10 (6–17) response rate n = 37 (93%)	0.95
		Median (IQR) of VAS[b] *score: 0–100% of the time*			
Organizational/environmental characteristics *15 survey items*	4. Shared environmental factors *Survey items: 16, 19, 20, 26, 27 & 28.*	13 (7–21) response rate n = 285 (86%)	13 (7–21) response rate n = 249 (85%)	13 (10–22) response rate n = 36 (90%)	0.43
	5. Shared personnel factors *Survey items: 24 & 25.*	7 (0–24) response rate n = 216 (65%)	7 (0–25) response rate n = 184 (63%)	8 (0–15) response rate n = 32 (80%)	0.54
	6. Specific workplace factors for Paramedics *Survey items: 14, 17, 22 & 23.*	23 (13–34) response rate n = 249 (75%)	23 (13–34) response rate n = 249 (85%)	x	–
	7. Specific workplace factors for Triage Nurses *Survey items: 15, 18 & 21.*	8 (3–17) response rate n = 35 (11%)	x	8 (3–17) response rate n = 35 (88%)	–
		Median (IQR) of VAS[b] *score: 0–100% of the time*			
Points of contact and communication *11 survey items*	8. Poor handover in the frontline environment *Survey items: 51.1, 51.2 & 51.3 (Reversed).*	10 (5–24) response rate n = 253 (76%)	11 (5–20) response rate n = 221 (75%)	5 (0–14) response rate n = 32 (80%)	<0.001*
	9. Poor handover in the Cath Lab environment *Survey items: 52.1, 52.2 & 52.3 (Reversed).*	12 (5–28) response rate n = 194 (58%)	12 (5–27) response rate n = 175 (60%)	10 (5–34) response rate n = 19 (48%)	0.66
	10. Lack of feedback *Survey items: 48, 49 & 50 (Reversed).*	24 (8–50) response rate n = 250 (75%)	24 (7–50) response rate n = 219 (75%)	17 (8–51) response rate n = 31 (78%)	0.56
	11. Untimely access to clinical support *Survey items: 46 & 47 (Reversed).*	20 (5–50) response rate n = 254 (76%)	24 (7–50) response rate n = 222 (76%)	7 (0–16) response rate n = 32 (80%)	<0.001*
		Median (IQR) of VAS[b] *score: 0–100% confident*			
Levels of confidence *17 survey items*	12. Lack of confidence in symptom assessment *Survey items: 29 - 32.*	19 (8–30) response rate n = 270 (81%)	18 (8–28) response rate n = 235 (80%)	23 (8–42) response rate n = 35 (88%)	0.21
	13. Lack of confidence in clinical assessment *Survey items: 40 - 45.*	11 (5–21) response rate n = 267 (80%)	11 (5–20) response rate n = 232 (79%)	14 (6–26) response rate n = 35 (88%)	0.39
	14. Lack of confidence in unique ECG patterns *Survey items: 34 - 39.*	19 (7–37) response rate n = 254 (80%)	20 (8–37) response rate n = 234 (80%)	11 (4–26) response rate n = 34 (85%)	0.03*

[a] NB.no respondents answered option 'don't know' or 'not applicable'.
[b] Visual analogue scale.
[c] Student's *t*-test or Mann U Whitney.
* Statistically significant.

[14]. The Magid et al. study had suggested the reworking of processes of care would improve flow of information [15]. Our results could also be explained by the distinctively different organisational environments these professionals operate within; paramedics function under one unified structure, Emergency nurses operate within larger heterogenic organisational structures. Furthermore, paramedics reported 'untimely access to clinical access and lack of confidence in diagnosing unique ECG patterns more often than emergency nurses. This finding could reflect the semi-autonomous position paramedics find themselves operating in before having access to hospital services.

There were significant differences in the frequency of experiencing six of the fourteen types of barriers according to where the respondent worked. Notably, regional/rural clinicians reported that 'lack of clinical skills development' and 'lack of feedback' affected STEMI management less often than they did for clinicians in metropolitan areas. This finding could reflect more personal communication that occurs in the smaller systems of care regional/rural clinicians operate within, where most clinicians know each other. However, regional/rural clinicians reported the guidelines were not achievable more often. This finding is likely to relate to the unavoidable geographical distances to field scene and hospital facilities for

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Table 3
Perceived Quantitative Barriers compared by geographical location.

Survey Section	Barrier Type after data reduction	All (n = 333)	Metro (n = 124)	Regional/Rural (n = 209)	p value[c]
		Mean ± SD score of a' No' response[a]			
Workplace policies and procedures *10 survey items*	1. Lack of Organisational/System Governance *Survey items: 1, 3, 4, 5, 6, 7 & 10 (Reversed).*	0.12 ± 0.17 response rate n = 308 (93%)	0.15 ± 0.19 response rate n = 114 (92%)	0.11 ± 0.17 response rate n = 194 (93%)	0.03*
	2. Lack of clinical skills development *Survey items: 2, 8 & 9 (Reversed).*	0.44 ± 0.36 response rate n = 306 (92%)	0.55 ± 0.33 response rate n = 114 (92%)	0.37 ± 0.35 response rate n = 192 (92%)	<0.001*
		Median (IQR) of VAS[b] score: 0–100% of the time			
Commitment to guideline *3 survey items*	3. Lack of belief in ACS guidelines *Survey items: 11, 12 & 13.*	10 (5–18) response rate n = 303 (91%)	8 (3–16) response rate n = 112 (90%)	11 (7–20) response rate n = 306 (91%)	0.03*
		Median (IQR) of VAS[b] score: 0–100% of the time			
Organizational/environmental characteristics *15 survey items*	4. Shared environmental factors *Survey items: 16, 19, 20, 26, 27 & 28.*	13 (7–21)response rate n = 285 (86%)	13 (9–21) response rate n = 106 (85%)	13 (6–21) response rate n = 179 (86%)	0.57
	5. Shared personnel factors *Survey items: 24 & 25.*	7 (0–24) response rate n = 216 (65%)	3 (0–13) response rate n = 79 (64%)	10 (1–25) response rate n = 137 (66%)	<0.01*
	6. Specific workplace factors for Paramedics *Survey items: 14, 17, 22 & 23.*	23 (13–34) response rate n = 249 (75%)	19 (10–28) response rate n = 102 (82%)	26 (14–38) response rate n = 175 (84%)	<0.001*
	7. Specific workplace factors for Triage Nurses *Survey items: 15, 18 & 21.*	8 (3–17) response rate n = 35 (11%)	6 (3–13) response rate n = 102 (82%)	10 (3–21) response rate n = 173 (83%)	0.02*
		Median (IQR) of VAS[b] score: 0–100% of the time			
Points of contact and communication *11 survey items*	8. Poor handover in the frontline environment *Survey items: 51.1, 51.2 & 51.3 (Reversed)*	10 (5–24) response rate n = 253 (76%)	11 (5–25) response rate n = 96 (77%)	10 (4–20) response rate n = 157 (75%)	0.32
	9. Poor handover in the Cath Lab environment *Survey items: 52.1, 52.2 & 52.3 (Reversed)*	12 (5–28) response rate n = 194 (58%)	12 (6–26) response rate n = 91 (73%)	11 (5–18) response rate n = 103 (49%)	0.57
	10. Lack of feedback *Survey items: 48, 49 & 50.*	24 (8–50) response rate n = 250 (75%)	27 (15–66) response rate n = 96 (77%)	19 (6–48) response rate n = 154 (74%)	0.04*
	11. Untimely access to clinical support *Survey items: 46 & 47.*	20 (5–50) response rate n = 254 (76%)	19 (5–57) response rate n = 96 (77%)	21 (5–49) response rate n = 158 (76%)	0.96
		Median (IQR) of VAS[b] score: 0–100% confident			
Levels of confidence *17 survey items*	12. Lack of confidence in symptom assessment *Survey items: 29 - 32.*	19 (8–30) response rate n = 270 (81%)	18 (9–31) response rate n = 102 (82%)	19 (8–31) response rate n = 168 (80%)	0.97
	13. Lack of confidence in clinical assessment *Survey items: 40 - 45.*	11 (5–21) response rate n = 267 (80%)	12 (5–23) response rate n = 102 (82%)	11 (5–23) response rate n = 165 (79%)	0.81
	14. Lack of confidence in unique ECG patterns *Survey items: 34 & 39.*	19 (7–37) response rate n = 254 (80%)	17 (7–34) response rate n = 102 (82%)	21 (8–38) response rate n = 166 (79%)	0.27

[a] NB. no respondents answered option 'don't know' or 'not applicable'.
[b] Visual analogue scale.
[c] Student's *t*-test or Mann U Whitney.
* Statistically significant.

regional and rural clinicians. This was a theme for these particular clinicians reiterated in their open-ended responses of the survey (Table A4).

These results identified a deficit in continuing professional development (CPD), lack of timely access to expert advice and the provision of clinical feedback to frontline clinicians. In the context of the relatively low confidence in assessing atypical symptomatology and to recognise unusual ECG patterns, these barriers take on particular clinical significance. Systematic feedback loops are known determinants of timely STEMI management [7]. Robust and timely feedback would add an educational component to the clinical context of a STEMI presentation, reinforcing and developing skills and confidence. The recent formation of a STEMI registry for patients utilising the services of AV when experiencing a STEMI has the potential to identify issues and develop strategies to to improve the feedback loop for paramedics [26].

There are several limitations to our findings. Firstly, to our knowledge there are no validated survey questions which address our research objectives; that is, to identify the most common barriers frontline clinicians experience when interacting with the presumed STEMI patient within a complex system of care operating across organisational boundaries. Therefore, we were required

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to design our own survey tool to gather data. Every effort was taken to ensure survey items were relevant to the known barriers, providing opportunity for respondents to 'self-report' the frequency of experiences and levels of confidence, primarily using the VAS scale, all of which was broadly guided by the theoretical domains framework. Secondly, the voluntary nature of participation in our study potentially introduced a self-selection bias to our findings [23]. Non-responder bias is also potentially a major confounder given the low response rates from both Paramedics (10%) and Victorian CENA members (9%). The reported geographical representation of responding paramedics may skew the results given there was a higher proportion of regional/rural responding to this survey. In addition, the proportion of CENA members who would be in the target population of all Victorian triage nurses is not known, and it was not feasible to gain ethics approval from every hospital to try to recruit triage nurses in their workplaces. A higher response rate would have been ideal to improve the generalizability of our findings, particularly for the emergency nursing cohort who are underrepresented given the total workforce of emergency nurses in Victoria. This low response rate aligns with similar Australian studies that have approached professional bodies to distribute surveys [27]. Thirdly, this survey was conducted during a period of process change to paramedic STEMI workflows. The implementation of the Cardiology consult advice hotline to support paramedic PHT may have alleviated anxiety around ECG interpretation and therefore underestimated our findings. Finally, this study was conducted in one state in Australia, therefore the variation in geography and population dispersion in other states may also limit the generalizability of these results.

Conclusion

This research has advanced an understanding of the challenges frontline clinicians experience. While barriers to timely management were not frequently experienced, this study highlights the need to improve workforce training and continuing professional development for all frontline clinicians. This could be addressed by integrating a robust systematic feedback structure for all clinicians. Frontline clinicians also require increased and timely access to expertise to improve confidence and support in clinical decision making. The potential flow-on effect of addressing these shortfalls could build collegiality and improve systems and health outcomes for all STEMI patients.

Conflicts of interest

We have no conflicts of interest. However, we recognise submission to this particular journal could be perceived as a potential conflict of interest for the journal due to the participation of CENA members in this research.

Authorship statement

LM, VL, DE, DC and OF conceived and designed the study. LM, VL, DE, MM and DS developed the study protocol. LM, VL designed and tested the study instruments. LM, VL, DS coordinated data collection. LM, VL, MM, DE analyzed the data. LM prepared first draft of the manuscript. VL, MM, OF, DC, DE, DS commented on subsequent drafts and approved the final version for publication.

Disclosures

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Associate Professsor Julia Morphet, Chair of Research Committee, College of Emergency Nursing Australasia.

Elizabeth Sinclair, Program Manager, Cardiac Reperfusion Strategy, Ambulance Victoria, Australia *(at the time of survey distribution)*.

To all survey participants from CENA (Victorian members) and Ambulance Victoria.

Appendix A

Table A1
FLUME survey (excluding demographic data).

Number	Survey Items	Possible Response
	Thinking of the environment in which you work most often (as indicated at the start of this survey), please answer the following questions.	
1	Does your workplace systematically measure the time it takes from 'first medical contact to first 12-lead ECG recording' for a patient complaining of chest pain?	Yes / No / Don't know/ NA
2	Does your workplace have a standardised checklist/decision aid to help triage a patient with chest pain?	Yes / No / Don't know/ NA
3	Does your workplace have a clinical practice guideline for the management of STEMI?	Yes / No / Don't know/ NA
4	Does your workplace utilise the pre-hospital notification system offered by Ambulance Victoria for STEMI patients who have a diagnostic 12-lead ECG in the field?	Yes / No / Don't know/ NA
5	Does your workplace systematically measure the time it takes from hospital arrival to treatment of the culprit vessel for STEMI patients (i.e. Door to Balloon Time or Door to Needle Time?)	Yes / No / Don't know/ NA
6	Does your workplace systematically measure the total time it takes to treat a STEMI patient from onset of symptoms to hospital arrival?	Yes / No / Don't know/ NA
7	Does your workplace systematically measure the total time it takes to transport a STEMI patient to hospital (i.e. call received to hospital arrival)?	Yes / No / Don't know/ NA
8	Does your workplace assess your ability to recognise a STEMI on a 12-lead ECG as part of your annual competency-based assessments?	Yes / No / Don't know/ NA
9	Does your workplace provide you with the opportunity to develop your skills in ECG recognition of STEMI in terms of continuing professional development?	Yes / No / Don't know/ NA
10	Are you aware of any other policies, procedures or protocols related to STEMI management that your organisation has that effect the way care is delivered?	Yes / No / Don't know/NA
	Please use this space if you would like to explain or elaborate on any of your answers to the questions above	open ended
11	Within your own work practice, do you believe the ACS guidelines of obtaining a 12-lead ECG within 10 minutes of first medical contact on patients with ischaemic pain are achievable	VAS 0 %–100 % of the time

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Table A1 (*Continued*)

Number	Survey Items	Possible Response
12	Within your own work practice, do you believe that treating STEMI patients within the guidelines of 90 minutes for primary PCI or 30 minutes for thrombolysis are achievable	VAS 0 %–100 % of the time
13	Do you believe that treating STEMI patients within the above timeframes make any difference to patient health outcomes	VAS 0 %–100 % of the time
	Please use this space if you would like to explain or elaborate on any of your answers to the questions above	open ended
14	How often in your workplace would the dispatch to a potential STEMI patient be miscoded according to your perceived opinion of the clinical situation	VAS 0 %–100 % of the time
15	How often in your workplace would the Triage score assigned to a potential STEMI patient be misclassified according to your perceived opinion of the clinical situation?	VAS 0 %–100 % of the time
16	How often in your workplace would there be difficulty persuading potential STEMI patients to be further assessed?	VAS 0 %–100 % of the time
17	How often in your workplace would there be difficulty transmitting the field 12-lead ECG to the destination hospital?	VAS 0 %–100 % of the time
18	How often in your workplace would there be no available 12-lead ECG machines to perform an ECG on a patient experiencing chest pain?	VAS 0 %–100 % of the time
19	How often in your workplace would there be an inappropriate environment to perform a 12-lead ECG on a patient experiencing chest pain (i.e. public area)?	VAS 0 %–100 % of the time
20	How often in your workplace would a 12-lead ECG be completed outside the recommended guideline of 10 minutes from first medical contact?	VAS 0 %–100 % of the time
21	How often in your workplace would there be difficulty activating the standard STEMI protocol/process?	VAS 0 %–100 % of the time
22	How often in your workplace would there be difficulty activating the standard STEMI clinical practice guideline within the AV organisation?	VAS 0 %–100 % of the time
23	How often in your workplace would there be difficulty activating the standard STEMI clinical practice guideline with the destination hospital? (i.e. clear STEMI criteria but destination hospital not activating the Cath Lab team?)	VAS 0 %–100 % of the time
24	How often in your workplace would there be an inadequate number of skilled personnel to recognise and treat a STEMI patient during business hours?	VAS 0 %–100 % of the time
25	How often in your workplace would there be an inadequate number of skilled personnel to recognise and treat a STEMI patient out of business hours?	VAS 0 %–100 % of the time
26	How often in your workplace would there be a missed STEMI diagnosis?	VAS 0 %–100 % of the time
27	How often would overcrowding in the Emergency Department impact upon the timely management of a potential STEMI patient?	VAS 0 %–100 % of the time
28	How often would fatigue from the workload of the current shift impact upon the timely management of the potential STEMI patient?	VAS 0 %–100 % of the time
	Please use this space if you would like to explain or elaborate on any of your answers in the questions above.	open ended
	Rate the level of confidence you have in diagnosing the following.	
29	A STEMI patient who provides a vague history of symptoms	VAS 0 %–100 % confident
30	A STEMI patient with typical ischaemic symptoms	VAS 0 %–100 % confident
31	A STEMI patient with atypical ischaemic symptoms	VAS 0 %–100 % confident
32	A STEMI patient with no ischaemic symptoms	VAS 0 %–100 % confident
	Rate the level of confidence you have in diagnosing a STEMI patient	
33	Using the algorithm interpretation of the 12-lead ECG print out	VAS 0 %–100 % confident
34	Who has a left bundle branch block (LBBB) on their 12-lead ECG	VAS 0 %–100 % confident
35	Who has a paced rhythm on their 12-lead ECG.	VAS 0 %–100 % confident
36	Who are in atrial fibrillation (AF) on their 12 lead ECG	VAS 0 %–100 % confident
37	Who have posterior ST segment changes on their 12-lead ECG.	VAS 0 %–100 % confident
38	Who have septal ST segment changes on their 12 lead ECG	VAS 0 %–100 % confident
39	Who have pathological Q waves present on their 12 lead ECG	VAS 0 %–100 % confident
	Rate the level of confidence you have in diagnosing STEMI patients.	
40	. . .who are over the age of 80 years of age.	VAS 0 %–100 % confident
41	. . ..who are female	VAS 0 %–100 % confident
42	. . .who have complex comorbid conditions (i.e. GORD, respiratory disease, diabetes).	VAS 0 %–100 % confident
43	. . .with a mental health issue (i.e schizophrenia)	VAS 0 %–100 % confident
44	. . .from a non-English speaking background	VAS 0 %–100 % confident
45	. . ...from a different cultural background to my own	VAS 0 %–100 % confident
	Please use this space if you would like to explain or elaborate on any of your answers to the questions above.	open ended
	Thinking of the environment in which you work most often (as indicated at the start of the survey), how often would the following happen in your workplace?	
46	Immediate access to advice of senior colleagues if unsure of a potential STEMI diagnosis.	VAS 0 %–100 % of the time
47	Immediate access to expert advice if unsure of a potential STEMI diagnosis	VAS 0 %–100 % of the time
48	Routine feedback given on general STEMI management performance	VAS 0 %–100 % of the time
49	Performance gaps in the treatment of STEMI are managed when identified	VAS 0 %–100 % of the time
50	I actively model best practice STEMI guidelines with my colleagues.	VAS 0 %–100 % of the time
	How often is clinical handover of the potential STEMI patient between the following disciplines efficient?	
	Paramedics - Triage/ED Nurses	VAS 0 %–100 % of the time
51	Paramedics - Cath Lab Staff	VAS 0 %–100 % of the time
	Triage/ED Nurses - Cath Lab Staff	VAS 0 %–100 % of the time
	How often is clinical handover of the potential STEMI patient between the following disciplines informative?	
	Paramedics - Triage/ED Nurses	VAS 0 %–100 % of the time
52	Paramedics - Cath Lab Staff	VAS 0 %–100 % of the time
	Triage/ED Nurses - Cath Lab Staff	VAS 0 %–100 % of the time
	Please use this space if you would like to explain or elaborate any of the answers for this section.	open ended
53	**What is the strongest barrier to timely STEMI management that you see or experience in your workplace?**	open ended
54	**What is the strongest facilitator to timely STEMI management that you see or experience in your workplace?**	open ended
55	**Are there any other barriers or facilitators to timely STEMI management that you experience that have not been described in this survey?**	open ended

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Table A2
Strongest barrier themes to timely STEMI management as described by all participants.

	Content Theme	Sample Quotes	Frequency N = 420 (%)
1	**Long distances to scene/hospital facilities**	*"Remote area therefore long travel time to the patient. MICA back up 50 min. away on a code 1, however we are now accredited in pre-hospital ALS thrombolysis"* ***(Paramedic).***	73 (17%)
2	**Hospital related delays/service provision**	*"I feel the biggest barrier is Cath Labs that have accepted but aren't ready on arrival (requiring the patient to be accepted by their ED). In these cases, there are often several other metropolitan receiving hospitals that are within the same transport time. I feel that if hospitals accept, they need to be more realistic about whether they can activate their Cath Lab team prior to the patient's arrival. If not, which is perfectly understandable in a busy system, it would be best to not accept and allow the patient to be transported to a facility that could provide immediate reperfusion on arrival." "Cath lab staff not being at the hospital by the time of arrival'.* ***(Paramedic).***	64 (15%)
3	**Lack of access to expert advice/resources**	*"Shortage of senior medical staff after hours and overnight, poor skills mix (nursing), particularly after hours"* ***(Nurse).*** *"Unskilled nursing and medical staff in urgent care. ANUMs have to push doctors to ring tertiary centre. Short staffed, no real clinical back up. No Cath lab on site"* ***(Nurse).***	47 (12%)
4	**Lack of experience/confidence in ECG interpretation**	*"Lack of experienced paramedics. Poor clinical approach and history taking can delay scene times and time to 12 lead acquisition. Most paramedics perform well though. Some will rely on the 12 lead and not use it in conjunction with the patient's presentation"* ***(Paramedic).***	30 (7%)
5	**Complicated/inefficient processes of care/communication**	*"Estimating time to Cath Lab. If no timelines all would be treated quicker"* ***(Paramedic).***	26 (6%)
6	**Specific paramedic barriers related to dispatch scene/ environment**	*"Dynamic workplace every scene is different"* ***(Paramedic).*** *"Delays in notification due to busy clinician radio channel"* ***(Paramedic).***. *"Difficult extrications from scenes with poorly designed houses"* ***(Paramedic).***	26 (6%)
7	**Technological delays**	*"Technology breakdown. Server not working, phone unpaired, etc"* ***(Paramedic).***	26 (6%)
8	**Lack of consensus of ECG diagnosis**	*"Disagreement about whether it is a STEMI and Cath Lab not being activated"* ***(Paramedic).*** *Deliberation over whether the patient is suitable for Cath Lab or not"* ***(Paramedic).*** *"Patient with borderline ECG presentations* ***(Nurse).***	21 (5%)
9	**Poor prioritization of clinical management**	*"Staff getting distracted by doing other tasks like putting in lines and stabilising patient"* ***(Nurse).*** *"Misunderstanding urgency to perform ECG on presentation"* ***(Nurse).***	21 (5%)
10	**Presenting out of business hours**	*"After hours activation of the Cath Lab from pre hospital Code STEMI pathway still fails - this requires the patient to be reassessed in the ED or await a cardiology review"* ***(Paramedic).*** *"Reluctance to activate Cath Lab, particularly overnight"* ***(Paramedic).***	20 (5%)
11	**Patient related factors at time of first medical contact**	*"Combative patient or family, difficult patient to manage, scene safety issues, environment issues, language or cultural barriers"* ***(Paramedic).*** "Getting enough information from patient to initiate a 12 lead ECG" ***(Paramedic).***	19 (5%)
12	**Patient delay in seeking treatment**	*"Delay in seeking medical advice/ help"* ***(Paramedic).***.	18 (5%)
13	**Lack of education/training**	*"Lack of education to recognize STEMI and make own diagnosis separate from Zoll monitor interpretation"* ***(Paramedic).*** *"Lack of in-depth ECG training for ALS paramedics"* ***(Paramedic).***	14 (3%)
14	**Overcrowding in ED**	*"Overcrowding in ED leading to delay in ECG"* ***(Nurse).***	13 (3%)

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Table A3
Top three barriers to timely STEMI management elicited from open-ended responses.

	Content Theme	Strongest barriers: all respondents *Sample Quotes*	Frequency *(N = 420)*
1	**Long distances to scene/hospital facilities**	*"Remote area therefore long travel time to the patient (sic). MICA back up 50 min. away on a code 1, however we are now accredited in pre-hospital ALS thrombolysis"* ***(Paramedic).***	73 (17%)
2	**Hospital related delays/service provision**	*"Time seems to stop if the patient gets transferred onto an ED trolley"* ***(Paramedic).***	64 (15%)
3	**Lack of access to expert advice/resources**	*"Timely access to our Clinician can be difficult if they are busy"* ***(Paramedic).***	47 (12%)
	Content Theme	Strongest barriers: paramedics *Sample Quotes*	Frequency *(N = 365)*
1	**Long distances to scene/hospital facilities**	*"Remote area therefore long travel time to the patient (sic). MICA back up 50 min. away on a code 1, however we are now accredited in pre-hospital ALS thrombolysis"*	72 (20%)
2	**Hospital related delays/service provision**	*"Time seems to stop if the patient gets transferred onto an ED trolley".*	57 (16%)
3	**Lack of access to expert advice/resources**	*"Timely access to our Clinician can be difficult if they are busy".*	42 (12%)
	Content Theme	Strongest barriers: Emergency Nurses *Sample Quotes*	Frequency *(N = 54)*
1	**Overcrowding in the Emergency Department**	*"Quantity of patients at triage and only 2 triage nurses. Often a line out the door so triage staff have to keep triaging even if they Give a CAT 2 to a patient for chest pain, often they can't perform the ECG within 10 minutes"*	10 (19%)
2	**Presenting out of business hours**	*"Reluctance to activate Cath Lab, particularly overnight".*	9 (17%)
3	**Hospital related delays/service provision**	*"Availability of Cath Lab"*	7 (13%)
	Content Theme	Strongest barriers: metropolitan clinicians *Sample Quotes*	Frequency *(N = 153)*
1	**Hospital related delays/service provision**	*"Time seems to stop if the patient gets transferred onto an ED trolley"* ***(Paramedic).***	30 (20%)
2	**Delays specific to paramedic**	*"lots of false dispatches"* ***(Paramedic).***	16 (10%)
3	**Presenting out of business hours**	*"Out of hours . . .calling in Cath lab staff can take time"* ***(Nurse).***	14 (9%)
	Content Theme	Strongest barriers: regional/rural clinicians *Sample Quotes*	Frequency *(N = 267)*
1	**Long distances to scene/hospital facilities**	*"Distance to scenes in rural settings"* ***(Paramedic).***	61 (23%)
2	**Lack of access to expert advice/resources**	*"Lack of GPs in smaller regional hospital willing to come into the hospital after hours/on call to accurately diagnose. Upon a nurse phone call"* ***(Paramedic).***	44 (16%)
3	**Hospital related delays/service provision**	"Outdated/ inefficient hospital practices and design" ***(Paramedic).***	34 (13%)

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Table A4
Top two themes derived from optional free-text response for each survey section.

Top Two Themes	*Sample Quote*	Total	Nurse	Paramedic	Metro	Regional / Rural
Survey Section 1: Workplace Policies & Procedures		***Frequency (N = 71 free text responses)***				
Well established STEMI protocols	"Multiple policies in AV regarding use of monitors, time critical patients and drug management" ***(Paramedic).***	44		31	12	13	32
Lack of 12-Lead ECG training	"Educated to rely on the machines' ECG interpretation - often have 12 leads that the monitor has interpreted as a STEMI but unable to see the changes on the ECG. Education around interpretation has been poor, very very basic. We have info cards we use in AV to help us determine when to notify etc which has been good" ***(Paramedic).***	6		5	2	1	4
Survey Section 2: Commitment to Guidelines		***Frequency (N = 61 free text responses)***				
Unachievable in certain situations	"Depends on distance or availability of Cath Labs / MICA backup" ***(Paramedic).***	30		23	7	7	23
Challenging to reach targets	"As a sole professional paramedic in a remote environment it is often difficult to achieve the timeframes" ***(Paramedic).***	19		19	0	0	19
Survey Section 3: Organizational / Environmental Characteristics		***Frequency (N = 65 free text responses)***				
Lack of availability of resources/equipment	"Again, it comes down to resources available, only 1 mica unit for our very large catchment area and very often not available, closest PCI facility is well outside the timeline" ***(Paramedic).***	15		14	1	1	14
Poor in hospital co-ordination	"There's is quite a variation between hospitals in metropolitan Melbourne in regard to timely STEMI management. Delays relate to 'off-loading' the patient in the emergency departments and a need to ". . .grab another ECG. . .despite receiving the faxed in-field graph and the patient being continuously monitored on the ambulance stretcher" ***(Paramedic).***.	14		14	7	0	7
Survey Section 4: Points of contact and communication		***Frequency (N = 24 free text responses)***				
Uninterested Cath Lab staff	"Cath Lab staff never appear interested in a handover from paramedics. They often ask specific questions but never allow the time for a detailed handover" ***(Paramedic).***	7		6	3	1	4
Poor communication structure in certain circumstances	"I think effective communication and collaboration is still one of the biggest barriers in effective patient care and outcomes" ***(Paramedic).***	5		2	3	2	2
Survey Section 5: Levels of confidence		***Frequency*** (N = 46 free text responses)				
Lower confidence in certain situations	"Difficulty with complex patients and management with contraindications and potential side effects effecting other pathologies" ***(Paramedic).***	17		12	6	5	11
Overdiagnosis/reliance of algorithm	"The ECG algorithm is often unhelpful. The obvious STEMI on ECG correlate heavily with the monitor, and do not require the assistance of the machine. The lesser levels of monitor surety can frequently indicate possible/potential STEMI and are incorrect" ***(Paramedic).***	13		13	5	0	8

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6.3 Chapter summary

This chapter presents the results from the cross-sectional FLUME survey of paramedics and emergency nurses in the Australian state of Victoria. To our knowledge there is no other study in the literature that explores the challenges for frontline clinicians in Australia.

Across the 14 types of barriers identified in the survey results, the most commonly occurring barriers to timely STEMI management for paramedics and emergency nurses were: 1) lack of clinical skills development; 2) lack of feedback; 3) untimely access to clinical support; 4) lack of confidence in symptom assessment; and 5) lack of confidence in unique ECG patterns. No new barriers or issues were identified in the responses to the open-ended questions.

There were differences in barriers experienced by paramedics and emergency nurses. Paramedics reported experiencing four types of barriers statistically significantly more frequently than emergency nurses. These four barriers were: 1) lack of organisational/system governance; 2) poor handover in the frontline environment; 3) untimely access to clinical support, and 4) lack of confidence in recognition of unique ECG patterns.

There were differences in barriers experienced by frontline clinicians in rural and metropolitan settings. Metropolitan-based clinicians were likely to experience the following barriers significantly more often that clinicians in rural settings: a lack of organisational/system governance; lack of clinical skills development; and lack of feedback. Rural clinicians were likely to experience the following barriers statistically significantly more often: lack of belief in ACS guidelines; shared personnel factors; specific workplace factors for paramedics, and specific workplace factors for emergency nurses.

The next chapter will be an integrative discussion of the findings from all three studies including their strengths and limitations.

CHAPTER 7: DISCUSSION

7.0 Chapter introduction

This thesis aimed to explore and describe STEMI management, including the relationship between recommended time parameters and health outcomes, and barriers and enablers to delivering timely treatment. Three studies were conducted to explore related questions. The first two studies analysed time parameters of STEMI management at a single metropolitan tertiary site. The third study surveyed frontline clinicians to explore perceived barriers to effective STEMI management in Victoria, Australia. This chapter will summarise the results of each study against the stated aims and research questions. This will provide the context for an integrated discussion that considers how the results of the studies together contribute to a better understanding of how timely STEMI management can be achieved. An outline of the contribution this body of work adds to existing literature will be presented, along with the individual strengths and limitations of the studies.

7.1 Study findings

A brief summary of the key findings of each study will be presented to provide context to the integrated discussion to follow. The first two studies of this thesis analysed time parameters of STEMI management at a single metropolitan tertiary site. The third study surveyed frontline clinicians to explore perceived barriers to effective STEMI management in Victoria, Australia.

Study I explored whether updated ESC target time parameters for STEMI management are achievable and influence health outcomes in a local setting. The results of Study 1 established the European STEMI performance targets were challenging to meet when compared to the Australian STEMI performance targets. Patients who achieved ESC targets parameters were more likely to be younger, present during business hours, present with pre-hospital notification and have no intubation prior to CCL arrival. Importantly, after adjusting for age and comorbid condition, meeting the ESC target parameters had no independent effect on one-year survival.

Study II explored the optimal time associated with the highest probability of achieving target time parameters for three separate parameters of care along the STEMI management continuum. The results of Study II identified the optimal time associated with achieving reperfusion targets for three particular timepoints of care along the continuum

of STEMI management: ‘Time to ECG’; ‘Time to CCL’; and ‘Time from symptom onset to FMC’. Differentiation was made between mode of presentation i.e. hospital presentation or PHN presentation to capture the contemporary processes of care used in STEMI management. For hospital presenters the optimal times identified were: ‘Door-ECG’ time of ≤7 minutes; ’Door-CCL’ time of ≤29 minutes; and ‘Symptom-onset-Door’ time of ≤99 minutes. For PHN presenters the optimal times identified were: ‘Field FMC-ECG’ time of ≤6 minutes, ‘Field FMC-CCL’ time of ≤51 minutes; and ‘Symptom-onset-Field FMC’ time of ≤108 minutes.

The quantile regression undertaken in Study II on each part of the STEMI time continuum identified several independent predictors that were associated with longer or shorter time to reperfusion. For hospital presenters, out of business hours and a ‘Door-ECG’ time > 7 minutes (the identified optimal time point) were associated with a longer time to reperfusion. For PHN presenters, out of business hour presentation, being intubated prior to Cardiac Catheter Laboratory arrival, distance to destination hospital and age ≥75 years were associated with longer time to reperfusion. Only two covariates were found to be associated with reducing time to reperfusion; they were male gender and having a ‘field FMC-ECG’ time > 18 minutes for the PHN presenter cohort.

Study III explored the perceived barriers to effective STEMI management as reported by frontline clinicians. The results of Study III identified fourteen types of barriers experienced by paramedics and triage nurses. The top five barrier types for all respondents were: ‘lack of clinical skills development’; ‘lack of feedback’; ‘lack of confidence in symptom assessment’; ‘lack of confidence in unique ECG patterns’; and ‘untimely access to clinical support’. When comparisons were made between professional groups; paramedics were more likely to report ‘untimely access to clinical support’ and lack of confidence in unique ECG patterns; and emergency nurses were more likely to report a lack of organisational/system governance. When comparisons were made between geographical location, clinicians in metropolitan areas were more likely to report a lack of clinical skills development and lack of feedback. While regional/rural clinicians were more likely to report a ‘lack of belief in ACS guidelines’, and regional/rural paramedics were more likely to report ‘specific workplace factors’, such as activating STEMI protocols with destination hospitals, and miscoding at dispatch. The open-ended responses of the survey consistently reiterated the above findings.

7.2 Synthesis of findings

While this thesis included three separate studies, all were designed to contribute to a better understanding of timely STEMI management. Common factors that affect timely STEMI management emerged across the three studies. Firstly, mode of presentation and time of presentation were identified in all three studies as factors in the delivery of timely STEMI management. Secondly, patient age and gender were found to prolong time to treatment in both Studies I and II. Thirdly, 'lack of confidence in symptom assessment', reported as one of the top five barriers in the FLUME survey, was reflected in the differences between the modes of presentation in Study II, with 'hospital presenters' more likely to have atypical symptomology. Lastly, the top two barriers reported by frontline clinicians in the FLUME survey, 'lack of clinical skills development and 'lack of feedback' highlight the need for system-based improvement, particularly when these factors are in direct contrast to the key features of position statements for STEMI performance by peak cardiology bodies. These will all be discussed further in the following.

Pre-hospital notification was a standout enabler to timely reperfusion in all three studies. Frontline clinicians reported the PHN system of care as one of the top three enablers to timely STEMI management in the FLUME survey. In Study I, there was a higher proportion of PHN presenters who achieved both the ESC targets and CSANZ targets (55% vs 95%, respectively) compared to hospital presenters (18% vs 57%, respectively). When the data was separated into discrete groups, PHN presenters were more likely to achieve ESC targets (OR 5.25, 95%CI 3.5-8.0; $p<0.001$). These findings were consistent with the current literature that demonstrate the benefit of utilising a pre-hospital presentation system of care in the Australian setting (Hutchison et al., 2013), and the global setting (Drew et al., 2011; Ting, Krumholz, et al., 2008).

Interestingly the divergence of the European guidelines in 2017 enabled a more comprehensive analysis of performance of the total STEMI population for this thesis by providing a specific target parameter to carry out analysis in Study II. Without this target, PHN presenters would have been excluded from analysis, as the CSANZ key performance targets measure time to reperfusion from hospital door for all STEMI patients and do not overtly mention field FMC time if presenting via PHN.

Another coherent and consistent theme observed throughout all three studies was time of presentation. Presenting out of business hours was a consistent barrier to timely STEMI management. For Study I, the proportion of patients achieving time to reperfusion targets in the out-of-hours scenario was noticeably less than patients presenting during business

hours. This was further affirmed by the fact that patients who presented during business hours were almost eight times more likely to achieve ESC performance targets (OR 7.9 95%CI 5.3-12; p<0.001). However, this finding did not translate to an impact on health outcomes when survival analysis was undertaken. Furthermore, exploration of explanatory variables using quantile regression for each part of Study II (except part two for hospital presenters) demonstrated that out of business hour presentations were consistently associated with increased time to treatment, adding between 7- 27 minutes to reperfusion times. These findings concurred with the known literature that demonstrate out-of-hours presentations are associated with prolonged time to reperfusion (Magid et al., 2005), but have little to no impact on short and long term health outcomes (Redfors et al., 2017; Tscharre et al., 2017). Time of presentation was also identified by frontline clinicians as a barrier to the delivery of timely STEMI management with presentation out of business hours reported as one of top three barriers across professional group and geographical location.

Gender had an ambiguous influence on timely STEMI management. Study I found no differences by gender in the univariate analysis comparing ESC targets vs CSANZ targets, nor did gender reach statistically significant findings for the subsequent multivariate analysis using logistic regression and cox proportional hazard modelling. However, when sub-group analysis was undertaken to better understand the influence gender had on time to treatment, statistically significant results were found (*see appendix 1*). Women were more likely to be older, present during business hours, via regular ambulance, with atypical symptoms, with higher comorbidity as determined by TIMI risk score, and more likely to fail time to reperfusion targets. However, these differences did not impact health outcomes when multivariate survival analysis was undertaken. After adjusting for age and a TIMI risk score >5, the model demonstrated gender was not a predictor of all cause one-year survival. These mortality results aligned with the findings of Murphy et al., (2019), van de Meer et al., (2015) and Movahed et al., (2009) that demonstrated all-cause mortality gender differences were explained by adjusting for older age and comorbid condition (Movahed et al., 2009; Murphy et al., 2019; van der Meer et al., 2015).

Furthermore, the results of Study II (Part One) demonstrated male gender was associated with shorter time to treatment. More specifically, male PHN presenters, were more likely to have a reduced ‘ECG-reperfusion’ time by 6 minutes (95% CI -10 to -0.3 minutes). These findings inversely concurred with literature reviewed earlier stating women were

more likely to have prolonged time to treatment in STEMI management (Khan et al., 2018; Movahed et al., 2009; Murphy et al., 2019; Stehli et al., 2019; van der Meer et al., 2015). Like gender, the age of a patient was also found to be associated with prolonged time to treatment for both Studies I and II. In multivariate analysis patients were more likely to achieve ESC performance targets if they were younger (OR 0.98, 95% CI 0.97-0.99 per year; p=0.04). Study II demonstrated age >75 years was independently associated with prolonged time to treatment for PHN presenters when analysing the effect time to ECG had on the proceeding time to reperfusion. These findings align with the literature that report older age requires evaluation of comorbid condition and the decision management should reflect consideration of general health, cognitive status and life expectancy (Alexander et al., 2007).

Presenting symptomology played a role in the provision of timely STEMI management for both Studies II and III. The baseline univariate analysis undertaken between mode of presentation in Study II demonstrated 'hospital presenters' were more likely to have atypical symptomology. Similarly, the FLUME survey identified 'lack of confidence in symptom assessment' as one of the top five barriers for frontline clinicians in delivering timely management. These findings aligned with literature that found variation and incongruence of symptoms impacted time to treatment at the frontline clinician level, namely absence of chest pain as an attenuating factor in the triaging of STEMI patients (Ryan et al., 2016), and when patient's symptoms were atypical in nature (Park et al., 2014; Pope et al., 2000).

The top two barriers reported in the FLUME survey, 'lack of clinical skills development' and 'lack of feedback', are reflective of insufficient organisational support in Victorian organisations that deliver STEMI management. These barriers also highlight the need to improve workforce training and continuing professional development, along with robust feedback mechanisms. These shortcomings highlight an opportunity to improve and strengthen healthcare systems by adopting some of the key strategies outlined in the literature. That is, to ensure a commitment to a permanent learning environment with senior management support (Curry et al., 2018; Maddox et al., 2017), implementing real-time feedback systems (Bradley, Herrin, et al., 2006).

7.3 Contribution to existing knowledge

All three studies individually contributed to the known literature in some capacity. Study I provided an extensive comparison between the divergent ESC and CSANZ STEMI

guidelines providing evidence that the more stringent ESC target parameters are challenging to achieve and have no impact on 12-month mortality. To my knowledge this is the first detailed analysis of the explicit changes to the ESC guideline undertaken on an Australian cohort. There is, however, a recent scientific letter briefly outlining a comparison of the ambiguous CSANZ reperfusion targets of 90 minutes vs 60 minutes of 1133 STEMI patients from a clinical outcome registry in Victoria, Australia. They reported a compliance rate of 69% vs 40% respectively for the CSANZ targets for all participating hospitals (Dinh et al., 2018). This aforementioned analysis did not delineate between mode of presentation and defined FMC as door time, therefore not capturing the PHN system of care in their analysis, unlike the methods employed in Study I.

The findings of Study II (Part 1) contributed to the limited evidence base for the ≤10 minute 'time to ECG' target espoused by the STEMI guidelines. This study built on the methodology used by Atzema et al., (2011) who analysed 'time to ECG' in patients receiving thrombolytic reperfusion agents on a multisite cohort. They identified the optimal time to ECG associated with achieving the reperfusion targets was 4 minutes (Atzema et al., 2011). In this thesis, similar statistical methodology was applied to multiple timeframes of care and the cohort separated by mode of presentation. The thesis analysis thus provided an expanded and comprehensive evaluation of the interaction between time points of care along the STEMI management continuum for both hospital presenters and PHN presenters.

Lastly, to my knowledge the findings from Study III are novel. There is no known literature exploring the challenges for frontline clinicians delivering STEMI management in Australia. There are examples of limited literature that have taken a wider lens in analysing operational systems and compliance with guidelines across the country of Turkey, finding most regions comply with STEMI guidelines and receive adequate institutional and peer support when treating STEMI patients (Kayipmaz et al., 2016). Other examples include a qualitative survey exploring barriers and facilitators for clinicians contributing to the delivery of pre-hospital thrombolysis, finding variation in perceptions of the practical aspects of delivering pre-hospital thrombolysis, and interestingly reported issues around the ownership and responsibility of the STEMI patient once the patient reached hospital (Rajabali et al., 2009). A larger survey of 3562 Emergency Department (ED) physicians across 65 hospitals broadly assessed design, management and support in ED with a particular focus on patient safety, finding a substantial need to improve inpatient coordination along with information coordination and consultation to maximise patient safety (Magid et al., 2009). These aforementioned studies have a broad application to

STEMI management, whereas our findings have specific implications for practice identifying and focusing on specific areas requiring improvement.

7.3 Strengths and limitations

The strengths and limitations of each study will be addressed individually to cover the broad scope of research questions and methodologies used. Strengths of this thesis are fourfold. Firstly, studies I and II use real-world data from a prospectively collected database at a high functioning university affiliated specialist hospital. This robust database has been maintained as part of a quality assurance program and monitored by dedicated clinical staff. The cohort of patients recorded in this HREC approved database are consecutive STEMI patients and inclusion/exclusion criteria are closely monitored. Synchronisation of the devices or computers used to document timepoint data occurs regularly.

Secondly, the comparison of the ESC versus CSANZ guidelines in Study I offered an in-depth analysis of the divergent guidelines, along with an insight into the potential areas of delay in the PHN system of care, currently not captured in the CSANZ guidelines. An understanding of this pre-hospital process of care is imperative as its utilisation is increasing with all metropolitan paramedics currently having 12-lead ECG capacity to transmit to destination hospitals.

Thirdly, the methodology used in Study II was suited to non-normally distributed data. The smoothing splines used to establish the initial relationship between time points then plotted against the estimated probability of achieving targets was one example. Splines fit nonparametric data by joining two or more polynomial curves, with the location of these joins known as knots (Wood, 2006). The second example was the use of quantile regression, which is considered a robust alternative to traditional multiple linear regression, particularly for skewed data, as it models the quantile, instead of the mean response on the predictors (Tarr, 2012).

Finally, the design and development of the FLUME survey in Study III was comprehensive. The survey design was informed by the Theoretical Domains Framework (TDF), an integrated model of theories for behavior change in implementing evidence based practice (Michie et al., 2005). The utilisation of this particular framework ensured item responses were thoughtfully representative of the possible barriers frontline clinicians

may perceive or experience as practitioners participating in complex workflows across organisational boundaries.

In contrast, the limitations of this thesis are threefold. Firstly, the data analysed for Studies I and II was derived from a single site cohort, limiting the possible generalisability of the overall findings. Secondly the data analysed in Study II only examines the endpoint of achieving reperfusion targets and does not address the health outcomes of these findings. The analyses would be strengthened using a larger multisite cohort that scrutinises health outcomes, such as rates of heart failure, readmission rates, long-term mortality and consumer feedback.

Thirdly, the limitations of the FLUME survey included lower than expected response rates from emergency nurses as outlined in the publication and the voluntary nature of participation in this survey, which may limit the generalisability of the findings.

7.4 Chapter summary

This chapter has provided an outline of key findings of each study, an integrative discussion of the common themes in the results from all three studies, the contribution the research makes to existing literature, and identified strengths and limitations of the analyses.

The following chapter will conclude this thesis.

CHAPTER 8: CONCLUSION

8.0 Chapter introduction

The final chapter will conclude the thesis by considering the implications for clinical practice, offering areas for future research and finish with a concluding statement.

8.1 Implications for clinical practice

The results from this thesis have given weight to several ways to improve timely STEMI management. Firstly, consideration to addressing the imbalance of time to treatment depending on time of presentation could be mitigated by extending the operational hours of the Cardiac Catheter Laboratory in the hospital in which the research was conducted. The total cohort of 922 consecutive STEMI patients analysed in this thesis presented 40% of the time during business hours and 60% out of business hours, with 30% of the out of business hour presentations on weekends or public holidays. Further evaluation in a subgroup demonstrated that during weekdays 9% of total patients presented out of business hours between 18:00hrs and 21:00hrs (*see appendix 8*). If operating hours of the Cardiac Catheter Laboratory were extended by another three hours during weekdays, 'in business hour' presentations could increase to almost 50% of all cases, potentially improving time to treatment. Alternative solutions include the optimisation of STEMI receiving centres to operate 24/7 with resourced capacity to provide an onsite STEMI service after hours. This, however, comes with a financial cost to the health system, requiring cost-benefit analysis to determine the impact such a change would have on health organisations and patient outcomes.

Secondly, the lack of skills development and feedback reported by the frontline clinicians in the FLUME survey indicate the need to improve continuing professional development and establish clearer clinical feedback mechanisms for the process of STEMI management. A meaningful performance feedback protocol with a component that actively engages the interest of the clinicians involved could address this need and provide simultaneous opportunity for continuing professional development.

8.2 Areas for future research

There are three areas of future research identified from this body of work. Firstly, the impact of long-term health outcomes for the calculated optimal FMC-ECG timeframes

identified in this thesis remains unanswered. There is opportunity to build on the work of Diercks et al., (2006) who is regularly cited as the evidence base for 'time to ECG' performance targets in the STEMI guidelines (Diercks et al., 2006). Applying the same methodology used in this thesis and based on Atzema et al., (2011) on a larger multisite cohort of registry data with access to 5-year outcomes, would address the impact on health outcomes. The current literature reports a study underway by Yiadom et al., (2018) outlining a protocol that aims to retrospectively measure the outcome differences associated with STEMI screening and diagnostic performance using the ≤10 minute performance target (Yiadom et al., 2018). In contrast, the proposal from this thesis would identify an optimal time to ECG and measure the associated impact on health outcomes offering a significant contribution to the limited published evidence base for the recommended 'FMC-ECG' time.

Secondly, the FLUME survey highlighted a disconnect in the facilitation of STEMI processes, poor access to expert advice/resources across organisational boundaries, a need for improved continuing professional development and clearer feedback mechanisms. The app-based communication tool for STEMI and stroke management being trialled in Victoria during the recruitment phase of the FLUME survey was consistently reported by clinicians as a technology that enabled effective STEMI management. To my knowledge this trial has been terminated with no further plans to proceed. This type of technology is imperative to invest in and evaluate from a public health resource perspective if optimisation and refinement of existing processes of care are to improve. An opportunity exists to partner and develop an app-based communication tool for both the paramedic organisations and health systems in Australia, to address the aforementioned barriers and evaluate its effectiveness.

Finally, there is a third factor for consideration and that is the patient's role in STEMI systems of care. While patient related delay has been well described and examined in the literature, the duration of ischemia prior to first medical contact is a major contributor to total ischemic time. Patient participation in their own care is an essential part of the equation in reducing this particular delay in time to treatment, with further research warranted in consumer codesign of systems of care to improve access and timeliness of STEMI management.

8.3 Conclusion

The combined findings from this PhD indicate that mode and time of presentation, advanced age, gender, lack of skills/development and feedback mechanisms all present challenges in the delivery of effective and efficient STEMI management. Robust system interventions, such as increasing the hours of operation of Cardiac Catheter Laboratories and introducing two-way communication and real time feedback for health professionals involved in STEMI management could help to address these challenges and strengthen existing processes of care.

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APPENDICES

Appendix 1: Gender subgroup analysis poster

Differences in characteristics, performance targets and outcomes for men and women with STEMI at a large tertiary Australian hospital.

Lorelle Martin[1,2], Maria Murphy[1,2], Omar Farouque[2,3], David Clark[2,3], David Edvardsson[1], Virginia Lewis[1].
1.School of Nursing and Midwifery, La Trobe University, Melbourne, Australia ; 2.Department of Cardiology, Austin Health, Melbourne, Australia ; 3. School of Medicine, University of Melbourne, Australia.

A recent comparison of gender in the management of STEMI found women experienced disparity in care and outcomes[1].

Literature suggests older age, atypical symptomology and higher comorbid condition at presentation may influence the management of women presenting with STEMI[2-4]. We were interested to know whether similar gender disparity existed at our institution.

Specific aims:

1. **Identify differences between men and women for characteristics, specific time points of care and health outcomes.**
2. **Predict whether these differences had an independent effect on mortality out to 365 days.**

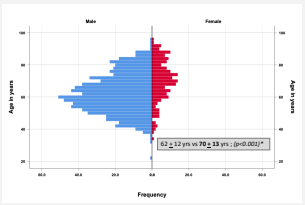
Methods:

A consecutive all-comer prospective cohort of 922 STEMI patients over nine years was analyzed. Gender differences were compared using Chi square analysis, Student's t-test or Mann-Whitney *u* test were appropriate. Cox proportion hazard modelling was used to determine independent predictors of 365-day mortality, controlling for age and comorbid status. Statistical significance was set at p< 0.05. All analyses: IBM SPSS for Mac, version 24 (IBM Corp., N.Y., USA).

Results:

Women represented 20% of the cohort and were eight years older when compared to men (*see Figure 1*).

Figure 1: Histogram of age by gender with univariate analysis.



*statistically significant using Student's t test

Differences were found between gender for several characteristics, outcomes and time points of care as outlined in Table 1 and illustrated in Figure 2.

Table 1: Univariate analysis of characteristics and outcomes.

	Male (n=737)	Female (n=185)	p value
In business hours *(0800-1800hrs Mon-Fri)*	270 (37%)	**88 (48%)**	p<0.01*
Out of business hours *(1800-0800hrs Mon-Fri, weekends)*	**467 (63%)**	97 (52%)	p<0.01*
Self-presentation	**155 (21%)**	25 (14%)	p=0.02*
Regular Ambulance presentation	183 (24%)	**78 (42%)**	p<0.001*
Pre-Hospital Notification Ambulance presentation	**399 (54%)**	82 (44%)	p=0.02*
Atypical symptomology ⁰	81 (11%)	**42 (23%)**	p<0.001*
Slow onset symptomology¹	225 (32%)	**73 (40%)**	p<0.03*
Assigned Triage score > 2	42 (6%)	**19 (11%)**	p<0.03*
Atrial Fibrillation on admission	33 (5%)	**20 (11%)**	p<0.01*
TIMI Risk score > 5	159 (22%)	**79 (43%)**	p<0.001*
Achieved time to treatment targets <90 minutes *n (%)*	**587 (80%)**	122 (66%)	p<0.001*
Symptom onset to Balloon time *median (Q1-Q3)*	188 (140-342)	**209 (153-378)**	p=0.03*
Length of stay in days *median (Q1-Q3)*	3.6 (3.0-4.3)	**4 (3.0-5.3)**	p<0.001**
In Hospital Mortality	39 (5.3%)	**21 (11.4%)**	p<0.01*
365-day Mortality	46 (6.2%)	**24 (13.0%)**	p<0.01*

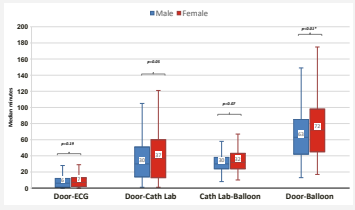
⁰ Back pain, fatigue, GI distress, palpitations, dizziness/faintness (Shin et al [5]); ¹ any typical or atypical pain that is gradual or intermittent in nature (O'Donnell et al [6]). *Statistically significant using chi square analysis; ** Statistically significant using Mann-Whitney u test.

Take home message

Our analysis found gender was not a predictor of 365-day mortality after controlling for age and comorbid risk.

Results: *continued*

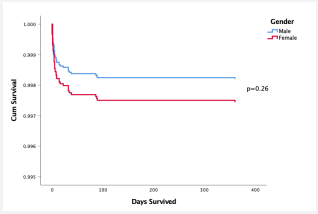
Figure 2: Specific time point data stratified by gender.



* Statistically significant using Mann-Whitney u testing

When multivariate survival analysis was undertaken adjusting for age and a TIMI risk score >5, the model demonstrated gender was not a predictor of all cause 365-day mortality. Women had a hazard ratio of 1.4 (95% CI 0.78-2.60); p=0.26 *(see Figure 3).*

Figure 3: Cox proportion hazard modelling for survival.



Model n=868, X^2 = 151.11, df=13, p<0.001

Conclusion:

Despite univariate differences in the cohort analysed , gender was not a predictor of mortality in multivariate regression. Limitations of this analysis include the use of single site observational cohort data. Further analysis could use a propensity score to match and examine the influence gender has on health outcomes on a larger sample size.

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5. Shin JY, Martin R, Howren MB. Influence of assessment methods on reports of gender differences in AMI symptoms. West J Nurs Res. 2009;31(5):553-68.
6. O'Donnell S, McKee G, Mooney M, O'Brien F, Moser DK. Slow-onset and fast-onset symptom presentations in acute coronary syndrome (ACS): new perspectives on prehospital delay in patients with ACS. J Emerg Med. 2014;46(4):507-15.

Acknowledgements: *this study was a subgroup analysis of a larger PhD research project on timely STEMI management supported by a NHMRC Post Graduate Scholarship (Grant Number APP1133322)*

E: lorelle.martin@latrobe.edu.au

Appendix 2: BMJ open submission confirmation

Submission Confirmation

Print

Thank you for your submission

Submitted to
BMJ Open

Manuscript ID
bmjopen-2020-038279

Title
An analysis of time to electrocardiogram (ECG) and STEMI reperfusion target times: a single tertiary site prospective analysis.

Authors
Martin, Lorelle
Lewis, Virginia
Shaker, Amanda
Murphy, Maria
Edvardsson, David
Clark, David
Farouque, Omar

Date Submitted
05-Mar-2020

Appendix 3: Ethics approval from La Trobe University

MARTIN, Lorelle

From: Human Ethics Low Risk - SHE [chesc.she@latrobe.edu.au]
Sent: Thursday, 23 February 2017 1:26 PM
To: Virginia Lewis
Cc: MARTIN, Lorelle
Subject: S17-011 Negligible risk Ethics application LEWIS - Accepted

LA TROBE UNIVERSITY

SHE COLLEGE HUMAN ETHICS SUBCOMMITTEE (SHE CHESC)

MEMORANDUM

To:	**Virginia Lewis**
Student:	**Lorelle Martin**
From:	**Secretariat, SHE College Human Ethics Sub-Committee (SHE CHESC)**
Reference:	**S17-011 - Ethics application for negligible risk project - accepted**
Title:	**"Revealing the Roadblocks in STEMI management" Timely ST-segment elevation myocardial infarction (STEMI) management of total ischaemic time in metropolitan, regional and rural Victoria.**
Date:	**23 February 2017**

The SHE CHESC Chair has evaluated your application as being of negligible risk and has accepted the project without review. The acceptance is for five years until 23/02/2022.

As a negligible-risk project (see Negligible risk guidelines), you are not required to submit annual and final reports, but you are required to maintain auditable records of the project.

Negligible risk studies cannot be modified using the Modification form, minor changes to a project do not require review. Researchers are responsible for informing the CHESC of any major modifications that may mean the research no longer fits the requirements of a negligible risk project. The Chief Investigator should send an email to the relevant CHESC entitled "modification for negligible risk project" with the project reference number (e.g. S16-500). Researchers will be informed via email if they are required to submit an application for human ethics review and approval to the CHESC or UHEC or if the modification is acceptable.

Please note that any data and consent forms need to be retained for a minimum of 5 years and that the consent forms must be stored separately from the data. Please also ensure that each participant retains a copy of the Participant Information Statement.

Kind regards,

Ms Kate Ferris MPH BPsych(Hons)
Human Ethics Officer
Secretariat – SHE College Human Ethics Sub-Committee
Ethics and Integrity / Research Office
La Trobe University Bundoora, Victoria 3086
M-F 9am – 5pm
T: 03 9479 3370 | M: 0437453309 | E: chesc.she@latrobe.edu.au
http://www.latrobe.edu.au/researchers/research-office/ethics/human-ethics
Research Office Reception +61 3 9479 1144
CRICOS Provider 00115M

1

Appendix 4: Ethics approval from CENA

ACN 102 951 799
228 Liverpool Street
HOBART TAS 7000
Tel: 03 6231 2722

Email: national@cena.org.au
Website: www.cena.org.au

23rd April 2017

Lorelle Martin
Cardiac Catheter Laboratory
Austin Health
Heidelberg 3084,
Melbourne, Victoria

Dear Lorelle,

On behalf of the Board of Directors and the Research Committee of the College of Emergency Nursing Australasia (CENA) I wish to advise you of our support to access the Victorian CENA membership for your study entitled; The FLUME survey.

In view of this support, CENA gives formal permission to place an advertisement via our e-blast system, which is emailed to our Victorian membership. You are also entitled to one reminder e-blast. The appropriate contact regarding circulating your call to participate is via Nikki, CENA Secretariat. Nikki's email is: national@cena.org.au.

The appropriate contact to publish the findings from this study is via Professor Ramon Shaban, Editor-in-Chief, Australasian Emergency Nursing Journal. Ramon's contact details are: editor@cena.org.au.

I would like to remind you that all publication outputs arising from CENA approved studies must include the following statement:

> *"This study was generously supported by the College of Emergency Nursing Australasia (CENA). The views of these researchers do not necessarily represent the views of CENA"*

It is the responsibility of the researcher(s) to maintain contact with the CENA Research committee Chair regarding any publications or presentations that arise out of the study.

We wish you well with this study and look forward to the findings and welcome future publications. If you have further questions please do not hesitate to contact me. Please quote the reference: **CENA/RC/2017/03** in future communication.

Kind Regards,

Dr Julia Morphet
CENA National Board/ Chair of Research Committee

Appendix 5: Ethics approval from Ambulance Victoria

AmbulanceVictoria

375 Manningham Road
Doncaster VIC 3108
PO Box 2000 Doncaster VIC 3108
T 03 9840 3500
ABN 50 373 327 705 004

7 APRIL 2017

File Ref: R17-003

Lorelle Martin
La Trobe University

Dear Lorelle,

Re: Research Proposal "R17-003: The FLUME survey: FrontLine clinicians survey to Understant delay in STEMI ManagEment" dated 14/02/2017.

I am pleased to inform you that Ambulance Victoria (AV) has approved participation in the above study, subject to return of a confidentiality deed.

Note that any changes to the original application will require submission of a protocol amendment to the AV Research Committee for consideration. Please ensure that AV is informed of any protocol changes as soon as possible.

As a component of ongoing communication processes, AV requires annual progress reports and a final report on completion of the study. You will be emailed the progress report approximately four weeks prior to the due date. Progress reports are required to be submitted by email.

Yours sincerely,

KAREN SMITH
Manager Research & Evaluation
On behalf of the Research Committee
Ambulance Victoria

Appendix 6: Ethics approval from Austin Health

Austin Health

Austin Hospital

145 Studley Road
PO Box 5555 Heidelberg
Victoria Australia 3084
Telephone 03 9496 5000
Facsimile 03 9458 4779
www.austin.org.au

Human Research Ethics Committee
Research Ethics Unit
Henry Buck Building
Austin Hospital

TO:	**Omar Farouque** **Department of Cardiology** **Level 5 North, Austin Tower** **Austin Health**
PROJECT:	Cardiac Catheterisation Laboratory Quality Assurance Audit
PROJECT NO:	H2011/04271
FROM:	**Jill Davis Research Ethics Unit Manager**
DATE:	1st April 2011
RE:	Audit application
Approval Period:	1st April 2011 – 1st April 2012

I wish to inform you that the audit named above has been reviewed and approved by the Austin Health Research Ethics Unit on behalf of the Austin Health Human Research Ethics Committee.

Should your audit not commence twelve (12) months from the date of this letter this approval will lapse. A resubmission to the Research Ethics Unit would then be necessary before you could commence.

Should you plan for your audit to go beyond the 1-year ethics approval, please request in writing an extension of ethics approval prior to its lapsing.

Please note a final report or publication must be submitted for all audits.

Jill Davis

Appendix 7: Ongoing ethics approval from Austin Health

Austin Hospital

145 Studley Road
PO Box 5555 Heidelberg
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Date: 3 July 2014

To: Ms Lorelle Martin
Cardiology Department, Austin Health

Project: **Door to balloon time in ST-elevation myocardial infarction Audit**

Project No: **LNR/14/Austin/320**

Approval Period: 1 year

Approval of Audit Activity

Document	*Version*	*Date*
Audit Activity Application incorporating the Protocol	1	14 May 2014

I wish to inform you that the audit application named above has been reviewed and approved by the Austin Health Office for Research on behalf of the Austin Health Human Research Ethics Committee.

An audit is defined as an activity instigated by an Austin Health Principal Investigator with the relevant expertise and experience, involving a research hypothesis which includes the analysis of data from previous collected patient information with an intention to publish or otherwise present the data beyond the staff of the hospital. Audits are generally retrospective reviews however prospective audits can be conducted in certain circumstances.

An audit does not involve the collection of new raw data (other than information that would ordinarily be collected as part of patient management) from a patient either in person, through a survey/questionnaire.

Should your audit not commence twelve (12) months from the date of this letter this approval will lapse. A resubmission to the Office for Research would then be necessary before you could commence.

Should you plan for your audit to go beyond the ethics approval period, please request in writing an extension of ethics approval prior to it lapsing.

Please note a final report must be submitted for all audits once completed.

Yours sincerely,

Victoria McMorran
Ethics Officer
Office for Research
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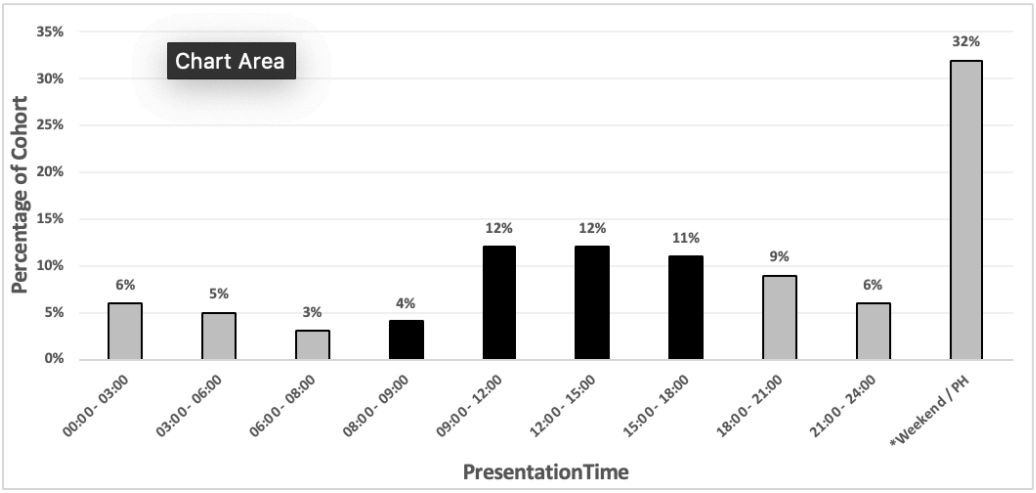
Phone: (03) 9496 3613 E-mail: ethics@austin.org.au

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice annotated with TGA comments (July 2008) and the applicable laws and regulations; and the Health Privacy Principles in The Health Record Act 2001.* The process this HREC uses to review multi-centre research proposals has been certified by the NHMRC.

Document name: Audit Activity approval Author: VM

Version Date: March 2014

Appendix 8: Distribution of patient arrival time to hospital



* PH = Public Holiday; ■ In business hours (39%); ▫ Out of business hours (61%)