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ORIGINAL RESEARCH

Prehospital Activation of the Cardiac Catheterization Laboratory in ST-Segment–Elevation Myocardial Infarction for Primary Percutaneous Coronary Intervention

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BACKGROUND: Prehospital activation of the cardiac catheter laboratory is associated with significant improvements in ST-segment–elevation myocardial infarction (STEMI) performance measures. However, there are equivocal data, particularly within Australia, regarding its influence on mortality. We assessed the association of prehospital activation on performance measures and mortality in patients with STEMI treated with primary percutaneous coronary intervention from the Queensland Cardiac Outcomes Registry (QCOR).

METHODS AND RESULTS: Consecutive ambulance-transported patients with STEMI treated with primary percutaneous coronary intervention were analyzed from January 1, 2017 to December 31, 2020 from the QCOR. The total and direct effects of prehospital activation on the primary outcomes (30-day and 1-year cardiovascular mortality) were estimated using logistic regression analyses. Secondary outcomes were STEMI performance measures. Among 2498 patients (mean age: 62.2±12.4 years; 79.2% male), 73% underwent prehospital activation. Median door-to-balloon time (34 minutes [26–46] versus 86 minutes [68–113]; *P*<0.001), first-electrocardiograph-to-balloon time (83.5 minutes [72–98] versus 109 minutes [81–139]; *P*<0.001), and proportion of patients meeting STEMI targets (door-to-balloon <60 minutes 90% versus 16%; *P*<0.001), electrocardiograph-to-balloon time <90 minutes (62% versus 33%; *P*<0.001) were significantly improved with prehospital activation. Prehospital activation was associated with significantly lower 30-day (1.6% versus 6.6%; *P*<0.001) and 1-year cardiovascular mortality (2.9% versus 9.5%; *P*<0.001). After adjustment, no prehospital activation was strongly associated with increased 30-day (odds ratio [OR], 3.6 [95% CI, 2.2–6.0], *P*<0.001) and 1-year cardiovascular mortality (OR, 3.0 [95% CI, 2.0–4.6]; *P*<0.001).

CONCLUSIONS: Prehospital activation of cardiac catheterization laboratory for primary percutaneous coronary intervention was associated with significantly shorter time to reperfusion, achievement of STEMI performance measures, and lower 30-day and 1-year cardiovascular mortality.

Key Words: direct transfer ■ prehospital activation ■ prehospital notification ■ primary PCI ■ ST-segment–elevation myocardial infarction ■ STEMI

Cardiovascular mortality remains one of the leading causes of death worldwide, with the majority of deaths occurring following acute myocardial infarctions.[1] Early identification and treatment of acute ST-segment–elevation myocardial infarction (STEMI) is crucial with the primary aim of minimizing the delay

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CLINICAL PERSPECTIVE

What Is New?

- In patients with ST-segment–elevation myocardial infarction, prehospital activation of the cardiac catheter laboratory and initiation of medical therapy is associated with shorter time to reperfusion, greater achievement of performance measures, and lower cardiovascular mortality.
- This study adds to the existing literature and demonstrates that a standardized prehospital activation strategy can be implemented on a large scale.

What Are the Clinical Implications?

- Widespread implementation of standardized prehospital activation strategies may offer opportunity to expedite ST-segment–elevation elevation myocardial infarction care and improve outcomes.

Nonstandard Abbreviations and Acronyms

CCL	cardiac catheterisation laboratory
DTB	door-to-balloon
FDECG	first diagnostic ECG
FMC	first medical contact

to reperfusion of the culprit coronary artery. The preferred method of reperfusion, if it can be achieved within 120 minutes of diagnosis, is primary percutaneous coronary intervention (PCI).[1] Historically, reducing the in-hospital delay to treatment or door-to-balloon (DTB) time has been the primary focus of improving outcomes in with primary PCI and is associated with lower short- and long-term mortality.[2–4] Several hospital-based strategies have seen significant reductions in median DTB times since their implementation.[5] However, despite these reductions in DTB, overall mortality following STEMI has not significantly improved over time with primary PCI.[2,4]

There has been a more recent shift to improve patient outcomes following STEMI by focusing on the collaboration with prehospital emergency medical services and incorporating strategies to reduce the prehospital delay to treatment. Implementation of several prehospital strategies both locally and internationally such as the Pre-Act initiative have demonstrated reductions in prehospital delays, further reductions in DTB time and total ischemic time, and reduced false positive cardiac catheterization laboratory (CCL) activations when protocol-driven prehospital STEMI pathways are implemented.[6–11] The impact of prehospital notification of STEMI and prehospital activation of the CCL on mortality, however, remains mixed with either lower[7,8,12–15] or equivalent[16,17] outcomes reported both across Australia and internationally. The Australian Acute Coronary Syndrome guidelines recommend primary PCI as the preferred reperfusion strategy if it can be performed within 90 minutes of first medical contact (FMC)[18] yet do not specify prehospital notification of STEMI by paramedics or prehospital activation of the CCL as strategies for achieving performance targets.

Significant variability exists in the design, implementation, and use of prehospital strategies particularly within Australia.[11,14,15] Prehospital emergency care within Queensland, Australia is provided by the Queensland Ambulance Service, which is a single, statewide, government-funded service. The statewide prehospital direct primary PCI referral pathway and prehospital activation strategy has been previously described in detail[14,19] (Figure S1). The aim of this study was to examine the impact of a well-established statewide prehospital activation strategy on achievement of STEMI performance measures and mortality in patients presenting with STEMI who received primary PCI.

METHODS

This multicenter study consisted of consecutive patients with STEMI over a 4-year period (January 1, 2017–December 31, 2020) who were transported by ambulance to 1 of 8 participating primary PCI facilities in Queensland (Figure S2) and underwent primary PCI. Queensland, a state within northeastern Australia, covers an area of over 1.8 million square kilometers (695 000 square miles) and serves a population of approximately 5.3 million people. Patients who experienced an in-hospital STEMI, underwent interhospital transfers, or self-presented were excluded from analysis. Patients with out-of-hospital cardiac arrest and emergency preprocedural intubation with unknown neurological status were also excluded (Figure 1). Comparisons were performed between ambulance-transported patients with STEMI who underwent the direct primary PCI referral and prehospital CCL activation pathway with ambulance-transported patients with STEMI who did not have direct primary PCI referral and prehospital activation of the CCL.

The statewide prehospital activation strategy involves STEMI diagnosis, PCI referral subject to reperfusion checklist (Figure S1), and initiation of medical therapy by paramedics upon direct telephone consultation with the on-call interventional cardiologist, who activates the CCL team before hospital arrival. Patient demographic characteristics, procedural variables, STEMI performance measures, and clinical end points of 30-day

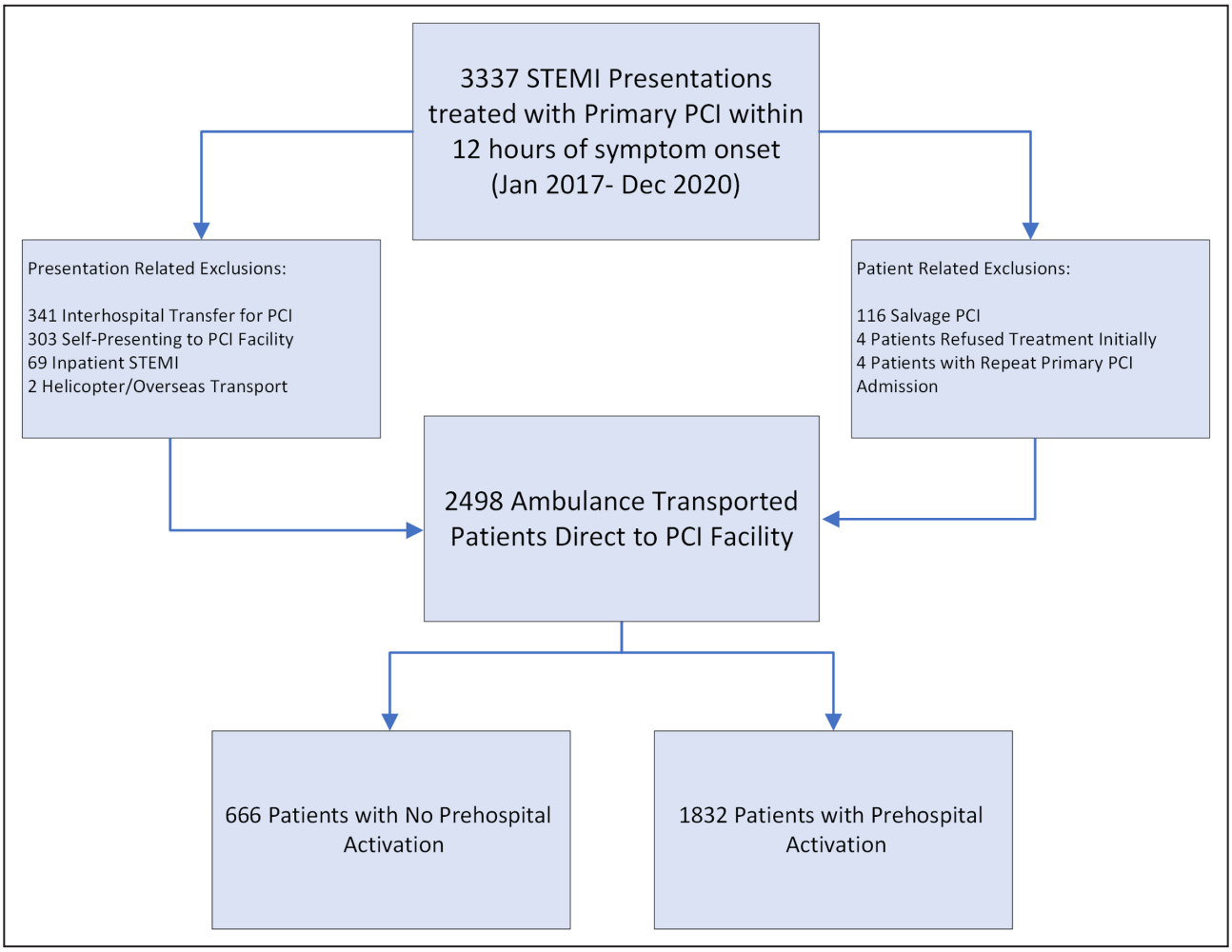

Figure 1. Study inclusion flow diagram.
Salvage PCI was defined as out-of-hospital cardiac arrest with emergency intubation. PCI indicates percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

mortality and 1-year mortality were compared between groups. Patients in this study who underwent prehospital activation pathway were administered prehospital concomitant antiplatelet therapy (aspirin 300 mg orally in combination with ticagrelor 180 mg orally or clopidogrel 600 mg orally) and anticoagulant therapy (heparin 5000 units intravenously) unless contraindicated, by the paramedics immediately post PCI referral. Those who did not undergo prehospital activation did not have administration of heparin nor ticagrelor/clopidogrel until review in the emergency department.

Data Sources

The Queensland Cardiac Outcomes Registry (QCOR) is a government-funded central, statewide data registry to which all public hospital cardiac catheter laboratories contribute patient information and procedural data. There are 8 public hospitals who participate, 3 metropolitan centers, and 5 regional centers (Figure S2). Patient demographics and periprocedural data were obtained from the QCOR and hospital electronic medical record, with data linkage from the Queensland Hospital Admitted Patient Data Collection from the Queensland Health Statistical Services Branch. Prehospital data were obtained from data linkage with the Queensland Ambulance Service STEMI database. Mortality and cause of death data were obtained using data linkage with the Queensland Registry of Births Deaths and Marriages. This study was approved by the Human Research Ethics Committee of the Prince Charles Hospital (LNR/2020/TPCH/75136) with a waiver of consent obtained. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the relevant data custodians within Queensland Health.

Data Definitions

DTB time was defined as the time in minutes from arrival at the PCI facility to the use of the first wire, balloon, or aspiration thrombectomy device in the PCI procedure. FMC for all patients was defined as initial paramedic contact. First diagnostic ECG (FDECG) was defined as the first ECG which demonstrated ST-segment changes consistent with the diagnosis of STEMI. Out of hours presentation was defined as between 1700 and 0800 hours during weekdays and during the weekend. Cardiovascular mortality was defined as any deaths resulting from the combination of ischemic heart disease, cardiac failure, cerebrovascular disease, peripheral artery disease, and aortic aneurysm.

Statistical Analysis

Continuous variables were compared between groups using an independent *t* test or Wilcoxon's rank-sum test as appropriate and categorical variables were compared using Pearson's chi-square test. Continuous variables were categorized using clinically meaningful cut-points. A causal diagram (Figure S3) was constructed a priori to depict postulated interrelationships between variables of interest, confounders, and mortality. The Dagitty[20] online user interface was used to select appropriate adjustment sets of covariates to estimate the total and direct effects of prehospital activation on 1-year mortality.[21] Confounders of interest in the relationship between prehospital activation and mortality comprised patient characteristics (age, sex) and presentation characteristics (cardiac arrest pre-PCI, regional hospital, out-of-hours presentation). Total effect estimates for the effect of prehospital activation on 30-day and 1-year mortality were derived from multivariable logistic regression models adjusted for confounders in the minimally sufficient adjustment set (age, sex, cardiac arrest pre-PCI, regional hospital, out-of-hours presentation) and direct effect estimates were additionally adjusted for the mediator (FDECG to balloon). Survival over time was explored graphically using Kaplan–Meier methods. Analyses were performed using the Stata statistical software package (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC).

RESULTS

Cohort Characteristics

A total of 2498 patients were included, of whom 1832 (73.3%) patients underwent prehospital activation and 666 (26.7%) who did not have prehospital activation. The mean age of the patients was 62.2 years (SD: 12.4) and 1978 (79.2%) were male (Table 1). The proportion of STEMI presentations receiving prehospital activation did not significantly differ over the study period (P=0.072). Patients with prehospital activation were more likely to be male, have dyslipidemia and less likely to have a cardiac arrest pre PCI (Table 1). The mean age, use of radial arterial access, and drug eluting stents were similar between groups and did not significantly change over the study period. Rates of Intra-aortic balloon pump and temporary pacing wire requirements were low and similar between groups. Prehospital activation was less likely to occur out of hours compared with in hours (out of hours 70% versus in hours 78%; P<0.001) and in regional centers (metropolitan 80% versus regional 65%; P<0.001). Regional and metropolitan centers are listed in Figure S2.

STEMI Performance Measures

Median DTB time was significantly shorter for patients with prehospital activation (34 versus 86 minutes; P<0.001) compared with those who did not have prehospital activation. Achievement of DTB<60 minutes (90% versus 16%; P<0.001) and FMC to balloon (43% versus 8%; P<0.001) and FDECG to balloon (62% versus 33%; P<0.001) targets were also both significantly improved with prehospital activation. Comparisons of total ischemic time and critical time points between groups are displayed (Figure 2). There was a 48-minute difference in median hospital door-to-CCL time in prehospital activation patients compared with those with no prehospital activation (12 versus 60 minutes; P<0.001). There was also a small yet significant difference in median CCL to balloon time (23 versus 25 minutes; P<0.001) in the prehospital activation cohort. There was a 47-minute median reduction in FMC to balloon and 67-minute median reduction in in overall ischemic time (symptom to balloon) with prehospital activation (Figure 2). Significant differences were seen in achievement of DTB<60 minutes both in hours and out of hours with prehospital activation associated with significant and comparable reductions in median DTB times (in hours 74 versus 29 minutes; P<0.001; out of hours 90 versus 39 minutes; P<0.001; Table 2).

Mortality

Of 2498 patients, 74 (3.0%) died within 30 days (all cardiovascular cause) and 130 (5.2%) died within 1 year of the index procedure. Overall unadjusted 30-day mortality was significantly higher for patients who did not have prehospital activation compared with patients who had prehospital activation (6.6% versus 1.6%; P<0.001). Similarly, 1-year all-cause mortality was significantly higher for those who did not have prehospital activation (10.2% versus 3.4%; P<0.001). One-year cardiovascular mortality was 4.2% and significantly higher for those who did not have prehospital

Table 1. Summary Statistics for Patient Characteristics by Prehospital Activation Pathway

Variable	Category	Total (n=2498)	No prehospital activation (n=666)	Prehospital activation (n=1832)	*P* value
Age*, y		62.2 (12.4)	62.8 (13.5)	62.0 (11.9)	0.170
Male sex†		1978 (79.2%)	507 (76.1%)	1471 (80.3%)	0.023
Weight‡, kg		84 (72–95)	84 (70–95)	83 (73–95)	0.400
Body mass index†, kg/m^2		27.7 (24.8–31.0)	27.5 (24.6–31.0)	27.7 (24.8–31.0)	0.510
Year of admission†					0.072
	2017	617 (24.7%)	189 (28.4%)	428 (23.4%)	
	2018	583 (23.3%)	153 (23.0%)	430 (23.5%)	
	2019	587 (23.5%)	145 (21.8%)	442 (24.1%)	
	2020	711 (28.5%)	179 (26.9%)	532 (29.0%)	
Geography†					<0.001
	Regional	1096 (43.9%)	385 (35.1%)	711 (64.9%)	
	Metropolitan	1402 (56.1%)	281 (20.0%)	1121 (80.0%)	
Presentation characteristics†					
Anterior infarction		982 (39.3%)	269 (40.4%)	713 (38.9%)	0.510
Multivessel disease		764 (30.6%)	196 (29.4%)	568 (31.0%)	0.447
Multivessel PCI		136 (5.4%)	38 (5.7%)	98 (5.4%)	0.732
Arterial approach					0.057
	Radial	1793 (71.8%)	497 (74.6%)	1296 (70.7%)	
	Femoral	705 (28.2%)	169 (25.4%)	536 (29.3%)	
Stent type					0.200
	No stent	152 (6.1%)	41 (6.2%)	111 (6.1%)	
	Bare metal	245 (9.8%)	77 (11.6%)	168 (9.2%)	
	Drug eluting	2101 (84.1%)	548 (82.3%)	1553 (84.8%)	
Out of hours		1528 (61.2%)	455 (68.3%)	1073 (58.6%)	<0.001
Weekend		708 (28.3%)	205 (30.8%)	503 (27.5%)	0.106
Cardiac arrest pre PCI		139 (5.6%)	59 (8.9%)	80 (4.4%)	<0.001
Temporary pacing		38 (1.5%)	14 (2.1%)	24 (1.3%)	0.154
Intra-aortic balloon pump		48 (1.9%)	14 (2.1%)	34 (1.9%)	0.690
Periprocedure cardiopulmonary resuscitation		21 (0.8%)	7 (1.1%)	14 (0.8%)	0.489
Cardiovascular history and risk factors†					
Previous myocardial infarction		142 (5.7%)	36 (5.4%)	106 (5.8%)	0.713
Previous coronary artery bypass grafting		33 (1.3%)	10 (1.5%)	23 (1.3%)	0.636
Previous PCI		229 (9.2%)	64 (9.6%)	165 (9.0%)	0.649
Diabetes		525 (21.0%)	157 (23.6%)	368 (20.1%)	0.060
Hypertension		865 (34.6%)	226 (33.9%)	639 (34.9%)	0.649
Dyslipidemia		743 (29.7%)	164 (24.6%)	579 (31.6%)	<0.001
Any smoking history		1654 (66.2%)	430 (64.6%)	1224 (66.8%)	0.281
Current smoker		958 (38.4%)	252 (37.8%)	706 (38.5%)	0.738
Left ventricular ejection fraction* (n=1847)		47.7 (11.6)	47.3 (12.6)	47.8 (11.3)	0.357

*Mean (SD) with *P* value derived from Student's *t* test, † n (%) with *P* value derived from Pearson's chi-square test or ‡ median (interquartile range) with *P* value from Wilcoxon's rank-sum test. PCI indicates percutaneous coronary intervention.

activation (8.6% versus 2.6%; *P*<0.001). Based on summary statistics (Table 3), variables with strong unadjusted associations with 1-year mortality included age, diabetes, radial arterial access, drug-eluting stent usage, cardiac arrest pre PCI, and FDECG to balloon time. After adjustment, patients who did not have prehospital activation were still at significantly increased risk of 30-day mortality compared with patients who

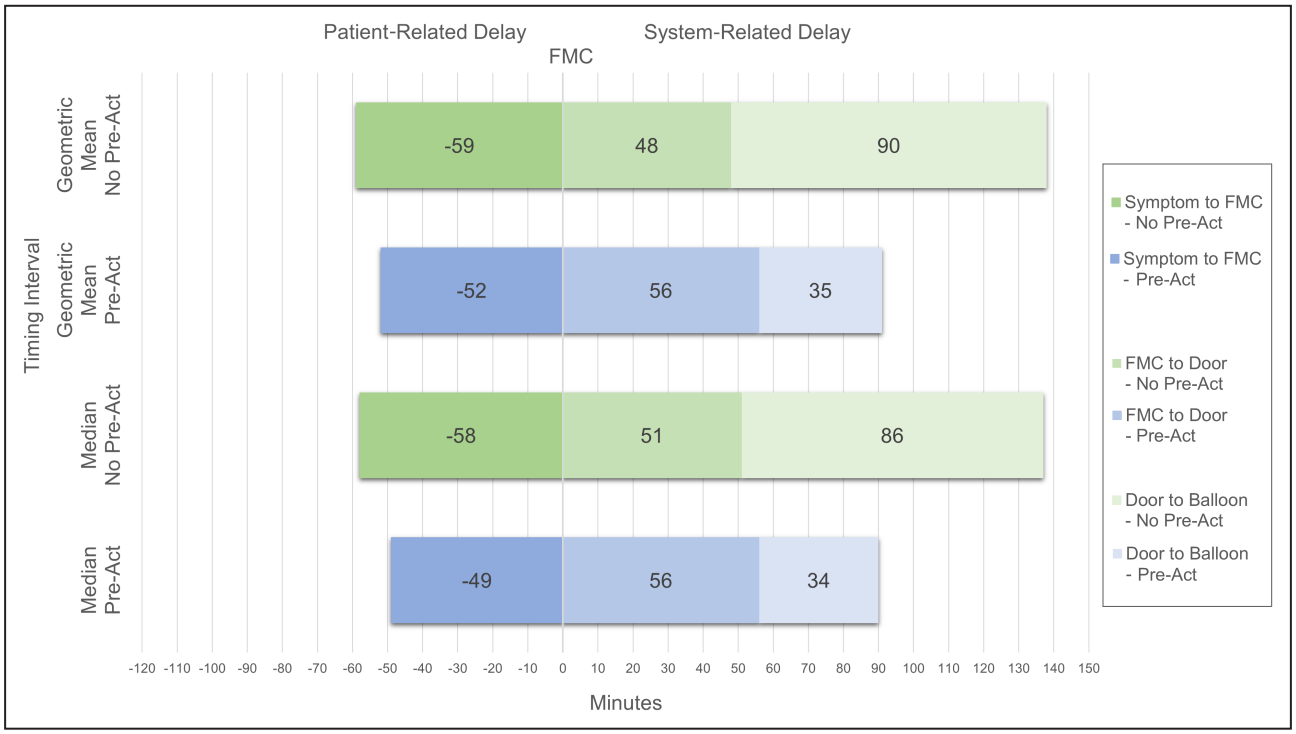

Figure 2. Comparison of geometric mean and median critical timepoints of ambulance-transported STEMI patients undergoing primary PCI for STEMI.
Prehospital activation cohort highlighted in blue. No prehospital activation cohort highlighted in green. Median and geometric mean times were similar across groups. Median time difference was 9 minutes shorter symptom onset to FMC, 5 min longer FMC-to-door time, and 52 min shorter DTB time with prehospital activation. FMC indicates first medical contact; PCI, percutaneous coronary intervention; Pre-Act, prehospital activation; and STEMI, ST-segment–elevation myocardial infarction.

had prehospital activation (total effect: odds ratio [OR], 3.6 [95% CI, 2.2–6.0], P<0.001; direct effect: OR, 2.9 [95% CI, 1.7–4.9], P<0.001), 1-year all-cause mortality (total effect: OR, 2.8 [95% CI, 1.9–4.1], P<0.001; direct effect: OR, 2.4 [95% CI, 1.6–3.6], P<0.001) and 1-year cardiovascular mortality (total effect: OR, 3.0 [95% CI, 2.1–5.1], P<0.001; direct effect: OR, 2.4 [95% CI, 1.5–3.8], P<0.001; Table 4). Nelson-Aalen survival estimates by prehospital notification group are presented graphically in Figure 3. Consistent with the logistic regression results, there was markedly increased early mortality risk for those without prehospital activation compared with those with prehospital activation. After excluding the initial 30-day period, the difference in survival between groups among those who survived at least 30 days was not statistically significant (hazard ratio [HR], 1.3 [95% CI, 0.9–2.1], P=0.21).

DISCUSSION

This statewide multicenter registry study highlights the low mortality rates and significant improvements in STEMI performance measures associated with patients who underwent ambulance prehospital activation and direct catheterization laboratory transfer for STEMI. Previously published literature regarding the impact of prehospital activation of patients with STEMI are consistent with the findings of this study with the consensus that there are significantly improved STEMI performance metrics.[8,9,11,12,15,22] Although the literature is predominantly supportive of lower mortality associated with prehospital activation strategies,[8,12–15] recently published data were suggestive of no mortality benefit with a prehospital notification strategy.[16,17] The published literature from Australia regarding mortality is mixed with national data showing lower mortality with ambulance transported patients compared with those who self-present in the Global Registry of Acute Coronary Events (GRACE) and Cooperative National Registry of Acute Coronary Care, Guideline Adherence, and Clinical Events (CONCORDANCE) registries.[23] More recent data from Victoria, however, highlighted lower mortality with patients who self-presented compared with ambulance-transported patients; however, there were significantly greater comorbidities, higher rates of cardiogenic shock, and mechanical ventricular support in the ambulance transported groups in this cohort study.[17] The increased risk of mortality associated with no prehospital activation in our study is

Table 2. Comparison of Summary Statistics* for STEMI Performance Measures by Prehospital Activation Pathway

Variable	Total (n=2498)	No prehospital activation (n=666)	Prehospital activation (n=1832)	*P* value
Symptom onset to FMC, min	51 (26–111)	58 (29–126)	49 (26–106)	0.004
FMC to FDECG, min	7 (4–15)	13 (5–52)	7 (4–11)	<0.001
FMC to door, min	55 (45–67)	51 (40–64)	56 (47–67)	<0.001
FMC to balloon, min	101 (84–127)	140 (115–176)	93 (80–109)	<0.001
Symptom onset to balloon, min	165 (128–238)	217 (168–295)	150 (121–208)	<0.001
Door to table, min	18 (9–40)	60 (46–85)	12 (7–22)	<0.001
Table to balloon, min	24 (19–30)	25 (20–31)	23 (19–29)	<0.001
DTB, min	42 (29–67)	86 (68–113)	34 (26–46)	<0.001
FDECG to balloon, min	87 (73–108)	109 (81–139)	83 (72–98)	<0.001
FMC to balloon <90 min	833 (33.3%)	52 (7.8%)	781 (42.6%)	<0.001
FDECG to balloon <90 min	1363 (54.6%)	222 (33.3%)	1141 (62.3%)	<0.001
DTB <60 min	1752 (70.1%)	107 (16.1%)	1645 (89.8%)	<0.001
IH DTB, min	33 (25–52)	74 (54–105)	29 (23–38)	<0.001
OH DTB, min	47 (33–77)	90 (75–118)	39 (30–50)	<0.001
IH DTB <60 min	781 (80.5%)	70 (33.2%)	711 (93.7%)	<0.001
OH DTB <60 min	971 (63.5%)	37 (8.1%)	934 (87.0%)	<0.001

DTB indicates door to balloon; FDECG, first diagnostic ECG; FMC, first medical contact; IH, in hours; OH, out of hours; and STEMI, ST-segment–elevation myocardial infarction.

*Summary statistics are median (interquartile range) with *P* value from Wilcoxon's rank-sum test.

consistent with mortality estimates demonstrated in previous literature with increasing risk of mortality associated with delays to treatment.[24,25]

Prehospital antithrombotic medication has been associated with improved thrombolysis in myocardial infarction coronary grade flow before PCI, lower rates of 30-day stent thrombosis, and lower mortality[26–28] and may explain, in conjunction with lower time to reperfusion, the association with lower mortality with prehospital activation in our study compared with previously published Australian literature.[16,17] Although these studies did demonstrate similar reductions in time to reperfusion, it is unclear whether the timing of initiation of medical therapy, including antithrombotic medication may also contribute to the mortality differences. Other differences in mortality in previously reported studies may be due to reporting all-cause mortality rather than specifically cardiovascular mortality as well as the inclusion/exclusion of patients with cardiogenic shock, out-of-hospital cardiac arrest, and preprocedural intubation with uncertain neurological status. Our study excluded patients who had out-of-hospital cardiac arrest and preprocedural intubation with uncertain neurological status. These patients were deemed salvage due to the significantly high proportion of neurovascular mortality in this group despite appropriate cardiovascular reperfusion. However, the current study did not exclude patients with cardiogenic shock, which may develop with longer delays to treatment as noted in other studies.[17] Cardiac arrest before PCI was identified on the causal pathway and was incorporated into the multivariate analysis. Unlike previous studies, cause of death was also analyzed in our study and both all-cause and cardiovascular mortality showed lower rates associated with prehospital activation.

Significant reductions in all STEMI performance measures were associated with prehospital activation. Although the current Australian[18] and American College of Cardiology/American Heart Association STEMI[29] guidelines suggest the metric FMC to balloon, the European Society of Cardiology STEMI guidelines[1] have adopted a STEMI diagnosis to device time within 90 minutes as a performance measure. This study also incorporated the similar metric of FDECG to balloon time, as well as FMC to balloon, which may be a more achievable performance metric when compared with FMC to balloon especially when there is delayed ECG or evolving evidence of STEMI. There was a significant albeit small difference in our study in median time from FMC to FDECG between groups with noticeably shorter time in the prehospital activation cohort. This may be explained in part by evolving or delayed ECG evidence of STEMI; however, it is important to acknowledge that initial misdiagnosis of STEMI may contribute to this, despite prehospital activation being associated with lower false positive STEMI activations.[9,10,14] Prehospital activation had the largest system timing impact on DTB time (Figure 2). Although the focus has shifted to overall system delays, DTB time still provides actionable targets to hospitals and is directly affected

Table 3. Summary Statistics for Variables of Interest by 1-Year Cardiovascular Mortality Status

Variable	Total patients (n=2498)	No cardiovascular death (n=2369)	Cardiovascular death (n=105)	*P* value
Age*, y	62.2 (12.4)	61.8 (12.2)	71.1 (13.8)	<0.001
Male sex†	1978 (79.2%)	1900 (79.4%)	78 (74.0%)	0.208
Weight‡, kg	84.0 (72.0–95.0)	84.0 (73.0–95.0)	80.0 (67.5–90.5)	0.013
Body mass index‡, kg/m^2	27.7 (24.8–31.0)	27.7 (24.8–31.0)	26.6 (23.9–30.7)	0.103
Previous myocardial infarction†	142 (5.7%)	137 (5.7%)	5 (4.8%)	0.677
Previous PCI†	229 (9.2%)	214 (8.9%)	15 (14.3%)	0.063
Previous coronary artery bypass graft†	33 (1.3%)	32 (1.3%)	1 (1.0%)	0.735
Diabetes†	525 (21.0%)	494 (20.6%)	31 (29.5%)	0.029
Hypertension†	865 (34.6%)	822 (34.4%)	43 (41.0%)	0.164
Dyslipidemia†	743 (29.7%)	718 (30.0%)	25 (23.8%)	0.174
Current smoker†	958 (38.4%)	926 (38.7%)	31 (30.5%)	0.090
Radial access†	1793 (71.8%)	1729 (72.3%)	64 (61.0%)	0.012
Drug-eluting stent†	2100 (84.1%)	2023 (84.5%)	77 (73.3%)	0.002
Anterior infarction†	982 (39.3%)	916 (38.3%)	66 (62.9%)	<0.001
Cardiac arrest pre PCI†	139 (5.6%)	123 (5.1%)	16 (15.2%)	<0.001
Multivessel disease†	764 (30.6%)	720 (30.1%)	44 (41.9%)	0.010
Left ventricular ejection fraction %* (n=1847)	48 (12)	48 (11)	36 (14)	<0.001
Regional hospital†	1096 (43.9%)	1046 (43.7%)	50 (47.6%)	0.624
Out of hours†	1528 (61.2%)	1458 (60.9%)	70 (66.7%)	0.238
Weekend presentation†	708 (28.3%)	684 (28.6%)	24 (22.9%)	0.203
Prehospital activation†	1832 (73.3%)	1784 (74.6%)	48 (45.7%)	<0.001
Door to balloon‡, min	42 (29–67)	41 (29–65)	68 (38–94)	<0.001
First medical contact to balloon‡, min	101 (84–127)	100 (84–125)	128 (99–160)	<0.001
First diagnostic ECG to balloon‡, min	87 (73–108)	86 (73–106)	108 (87–140)	<0.001
Symptom to balloon‡, min	165 (128–238)	163 (127–237)	191 (146–260)	0.005

Summary statistics are * mean (SD) with *P* value derived from Student's *t* test, † n (%) with *P* value derived from Pearson's chi-square test, or ‡ median (interquartile range) with *P* value from Wilcoxon's rank-sum test. PCI indicates percutaneous coronary intervention.

by in-hospital processes. This metric can still be used to support in-hospital improvements and accountability.[30] Similar to previously published data there was a 5-minute difference in the median FMC-to-door time with patients who did not have prehospital activation being slightly faster (Figure 2). Additional workload performed by paramedics in the prehospital activation pathway (patient consent, primary PCI referral with the interventional cardiologist, and subsequent administering of medication), may account for these differences.

The proportion of patients with STEMI who are ambulance transported and have prehospital notification/activation reported in published Australian literature continues to remain low and constant with less than half of patients receiving prehospital notification.[9,16,23,31] This is significantly lower than current data presented in this study (73%). Recent international data from the United States are also suggestive of lower rates of prehospital activation compared with the current study with approximately 40% of patients having prehospital activation.[7] Key prehospital activation strategies used in Queensland are listed in Table 5. There were regional differences in the use of prehospital activation in our study that may be associated with numerous factors such as paramedic staffing and experience levels as well as other unobserved factors. Increasing the use of prehospital activation may be an opportunity to improve STEMI care in regional areas. Previous examination of predictors of prehospital notification and similar to our study demonstrated greater use of prehospital notification during in-hours,[17] yet unlike the predictors listed in this Victorian study, our study did not associate any sex-related differences with prehospital activation nor differences in the identified culprit coronary vessel. Previous literature examining sex differences in STEMI have suggested the use of standardized prehospital protocols reducing the differences in sex-related treatment discrepancies.[32,33]

This study adds to the support for standardized prehospital strategies incorporating prehospital notification of STEMI, initiation of medical therapy, and activation of the cardiac catheterization laboratory to improve STEMI performance measures, reduce overall time to reperfusion, and lower short- and longer-term mortality. Routine monitoring of prehospital activation

Table 4. Mortality Outcomes and Logistic Regression Modeling for the Effects of Prehospital Activation on 1-Year Cardiovascular Mortality

Outcome variable	Total (n=2498)	No prehospital activation (n=666)	Prehospital activation (n=1832)	*P* value
30-d All-cause mortality*	74 (3.0%)	44 (6.6%)	30 (1.6%)	<0.001
1-y All-cause mortality*	130 (5.2%)	68 (10.2%)	62 (3.4%)	<0.001
1-y Cardiovascular mortality*	105 (4.2%)	57 (8.6%)	48 (2.6%)	<0.001

Exposure variable	Category	Unadjusted effect		Direct effect†		Total effect†	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Prehospital activation	Yes	Reference		Reference		Reference	
	No	3.5 (2.3–5.2)	<0.001	2.3 (1.5–3.7)	<0.001	3.0 (2.0–4.6)	<0.001
Age, y			<0.001		<0.001		<0.001
	<66	Reference		Reference		Reference	
	65-<75	1.1 (0.7–2.0)	0.738	1.1 (0.6–2.0)	0.721	1.2 (0.7–2.1)	0.569
	≥75	5.3 (3.4–8.3)	<0.001	5.3 (3.3–8.4)	<0.001	5.7 (3.6–9.1)	<0.001
Cardiac arrest pre percutaneous coronary intervention	No	Reference		Reference		Reference	
	Yes	3.3 (1.9–5.8)	<0.001	3.2 (1.8–5.9)	<0.001	3.5 (1.9–6.3)	<0.001
Out of hours presentation	Yes	Reference		Reference		Reference	
	No	0.8 (0.5–1.2)	0.239	0.9 (0.6–1.4)	0.602	0.8 (0.5–1.3)	0.335
Sex	Female	Reference		Reference		Reference	
	Male	0.8 (0.5–1.2)	0.208	1.1 (0.7–1.8)	0.703	1.1 (0.7–1.7)	0.777
Regional hospital	No	Reference		Reference		Reference	
	Yes	1.2 (0.8–1.7)	0.430	0.9 (0.6–1.4)	0.731	0.8 (0.6–1.3)	0.388
First diagnostic ECG to balloon (min)			<0.001		0.016		
	<90	Reference		Reference			
	90-<120	1.5 (0.9–2.5)	0.130	1.2 (0.7–2.0)	0.559		
	≥120	4.3 (2.8–6.9)	<0.001	2.1 (1.2–3.7)	0.006		

*Summary statistics are n (%) with *P* value derived from Pearson's chi-square test.
†Note that inference should be limited to the exposure of interest; it is not appropriate to interpret the effects of other covariates in these multivariable models.
OR indicates odds ratio.

rates may provide opportunities to improve prehospital care in STEMI.

Strengths and Limitations

This is a multicenter study analyzing prospectively collected data from the QCOR registry in a large cohort of consecutive patients with STEMI treated with primary PCI. Despite our statistical methods used and due to the observational nature of this study, there may be unmeasured cofounders that could influence mortality. Although there may be unmeasured confounders, our study did have complete and high-quality measures for many important confounders related to cardiovascular outcomes as described in the causal pathway diagram. A comparison of total and direct effects involved in the association between prehospital activation and 1-year mortality enables us to better understand the causal pathways.

Selection bias may exist when identifying STEMI in the prehospital setting and may result in exclusion of ambiguous or evolving STEMI presentations or those patients where STEMI was not initially recognized, from the direct primary PCI referral pathway. Previously documented reasons for no prehospital activation include availability of critical care paramedics,[14] which may have contributed to the lower use of prehospital activation in more regional centers and after hours as well as proximity to hospital, which also may explain the significantly shorter FMC to hospital arrival time in the no-prehospital activation group.[34] Additionally, bypass of non-PCI facilities could contribute to longer prehospital travel times in the prehospital notification group and has been previously demonstrated to increase ambulance transport time.[35] Our study also compared only patients who underwent primary PCI for treatment of STEMI within 12 hours of symptom onset and patients with STEMI who were treated medically or with coronary artery bypass may add to potential bias. This study did not analyze secondary prevention measures such as postprocedural medication compliance or cardiac rehabilitation adherence, which may also influence longer-term mortality.

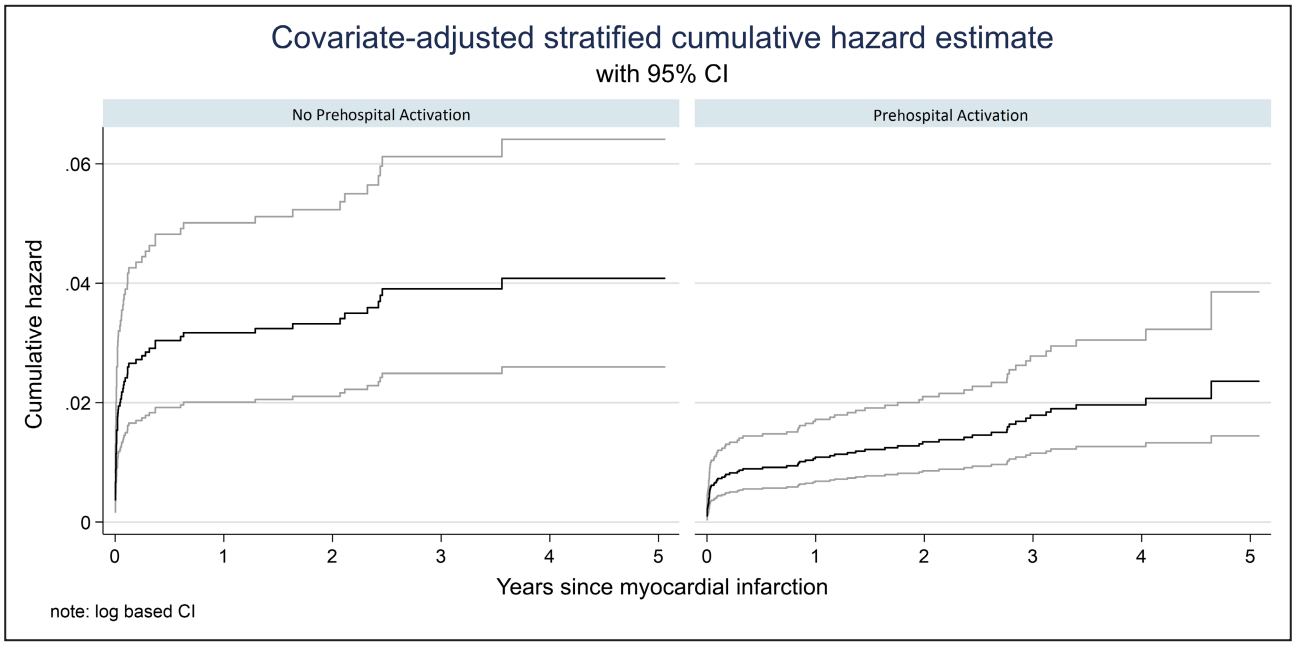

Figure 3. Adjusted cumulative hazard estimates for cardiovascular mortality with 95% CIs by prior hospital notification status.
Adjusted for age, sex, cardiac arrest pre-PCI, regional hospital, and out-of-hours presentation. PCI indicates percutaneous coronary intervention.

CONCLUSIONS

A standardized statewide strategy incorporating prehospital notification of STEMI, initiation of medical therapy, and prehospital activation of the cardiac catheter laboratory significantly improved STEMI performance measures, reduced total ischemic time, and is associated with lower 30-day and 1-year mortality. Widespread implementation of prehospital activation may offer significant opportunity to expedite STEMI care and improve outcomes.

Table 5. Key Prehospital Activation Strategies Used in Queensland

Queensland prehospital activation strategies
Prehospital ECG within 10 min of first medical contact
Paramedic interpretation of prehospital ECG with standardized statewide prehospital PCI referral checklist
Non-PCI facility bypass when ST-segment elevation myocardial infarction suspected
Direct telephone consultation and PCI referral to interventional cardiologist on call
Prehospital PCI medication given by ambulance officers at time of referral acceptance
CCL team activated only by interventional cardiologist
On-call team available within 30 min of activation
Direct transfer to CCL with emergency department bypass

CCL indicates cardiac catheterization laboratory; and PCI, percutaneous coronary intervention.

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Supplemental Material

Figures S1–S3

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SUPPLEMENTAL MATERIAL

Figure S1. Queensland Ambulance Service – Autonomous primary PCI referral Checklist.

Autonomous pPCI Referral Checklist *(April, 2018)*

PATIENT / CASE DETAILS			
Surname		**Given Name**	
Age		**Weight**	
Case Date		**Case Number**	

INDICATIONS FOR pPCI REFERRAL – if the answer is NO or UNSURE to ANY of the following, do NOT refer the patient for pPCI and do NOT administer the patient any heparin, ticagrelor or clopidogrel.	**Yes**	**No**	**Unsure**
Located < 60 minutes transport time (from time of first STEMI 12-Lead ECG) to a QAS approved pPCI capable hospital?			
GCS = 15?			
Classic ongoing ischaemic chest pain < 12 hours in duration? **Note: Atypical chest pain is excluded.**			
12-Lead ECG with persistent ST-elevation ≥ 1 mm in at least two contiguous limb leads **AND/OR** ≥ 2 mm in at least two contiguous chest leads V_1-V_6?			
Normal QRS width (< 0.12 seconds) OR right bundle branch block identified on the 12-Lead ECG?			
CONTRAINDICATIONS FOR pPCI REFERRAL – if the answer is YES or UNSURE to ANY of the following questions, do NOT refer the patient for pPCI and do NOT administer the patient any heparin, ticagrelor or clopidogrel.	**Yes**	**No**	**Unsure**
History of serious systemic disease (e.g. advanced/terminal cancer, severe liver or kidney disease)?			
Resident of an aged care facility requiring significant assistance with activities of daily living?			
Acute myocardial infarction in the setting of trauma?			
ABSOLUTE CONTRAINDICATIONS FOR HEPARIN ADMINISTRATION – if the answer is YES or UNSURE to ANY of the following the patient may still be referred for pPCI however, do NOT administer the patient heparin.	**Yes**	**No**	**Unsure**
Known severe adverse reaction to heparin?			
Patient < 18 years?			
Active bleeding (excluding menses) OR clotting disorder (e.g. haemophilia)?			
Prior intracranial haemorrhage?			
Current use of anticoagulants (e.g. apixaban, dabigatran, rivaroxaban, warfarin)?			
RELATIVE CONTRAINDICATIONS FOR HEPARIN ADMINISTRATION – if the answer is YES or UNSURE to ANY of the following the paramedic must consult the interventional cardiologist prior to heparin administration.	**Yes**	**No**	**Unsure**
Uncontrolled hypertension (systolic BP > 180 mmHg **AND/OR** diastolic BP > 110 mmHg at any stage during current acute episode)?			
Known cerebral disease, in particular a malignant intracranial neoplasm OR arteriovenous malformation?			
Ischaemic stroke OR Transient Ischaemic Attack (TIA) within last 3 months?			
History of significant closed head / facial trauma within last 3 months?			
History of major trauma or surgery (including laser eye surgery) within last 6 weeks?			

Autonomous pPCI Referral Checklist *(continued)*

CONTRAINDICATIONS FOR TICAGRELOR ADMINISTRATION – if the answer is YES or UNSURE to ANY of the following the patient may still be referred for pPCI however, do NOT administer the patient ticagrelor.	**Yes**	**No**	**Unsure**
Known severe adverse reaction to ticagrelor?			
Patient currently taking ticagrelor **OR** clopidogrel?			
Patient < 18 years?			
Active bleeding (excluding menses)?			
Prior intracranial haemorrhage?			
History of hepatic impairment?			
CONTRAINDICATIONS FOR CLOPIDOGREL ADMINISTRATION – if the answer is YES or UNSURE to ANY of the following the patient may still be referred for pPCI however, do NOT administer the patient clopidogrel.	**Yes**	**No**	**Unsure**
Known severe adverse reaction to clopidogrel?			
Patient currently taking clopidogrel **OR** ticagrelor?			
Patient < 18 years?			
Active bleeding (excluding menses)?			
Prior intracranial haemorrhage?			

CONSENT

All patients eligible for Autonomous pPCI Referral **MUST** read (or have read to them) the following information and if consent is given the patient must sign the bottom section of this form.

It is likely that you are suffering a heart attack. I would like to refer you to an interventional cardiologist for a procedure to restore cardiac blood flow. If this procedure is able to be performed the interventional cardiologist may request the following medications be administered with your consent:

- a drug which reduces new clot formation called heparin; **AND**
- either a drug called ticagrelor **OR** clopidogrel which will assist in maintaining cardiac blood flow.

Heparin **AND** either ticagrelor **OR** clopidogrel can cause significant bleeding in a small number of patients however, the use of these drugs is supported by national and international cardiology guidelines.

Medical Records: I give permission for the QAS to access my hospital record for information relating to this procedure.

Patient signature	**X** .....

PARAMEDIC DETAILS

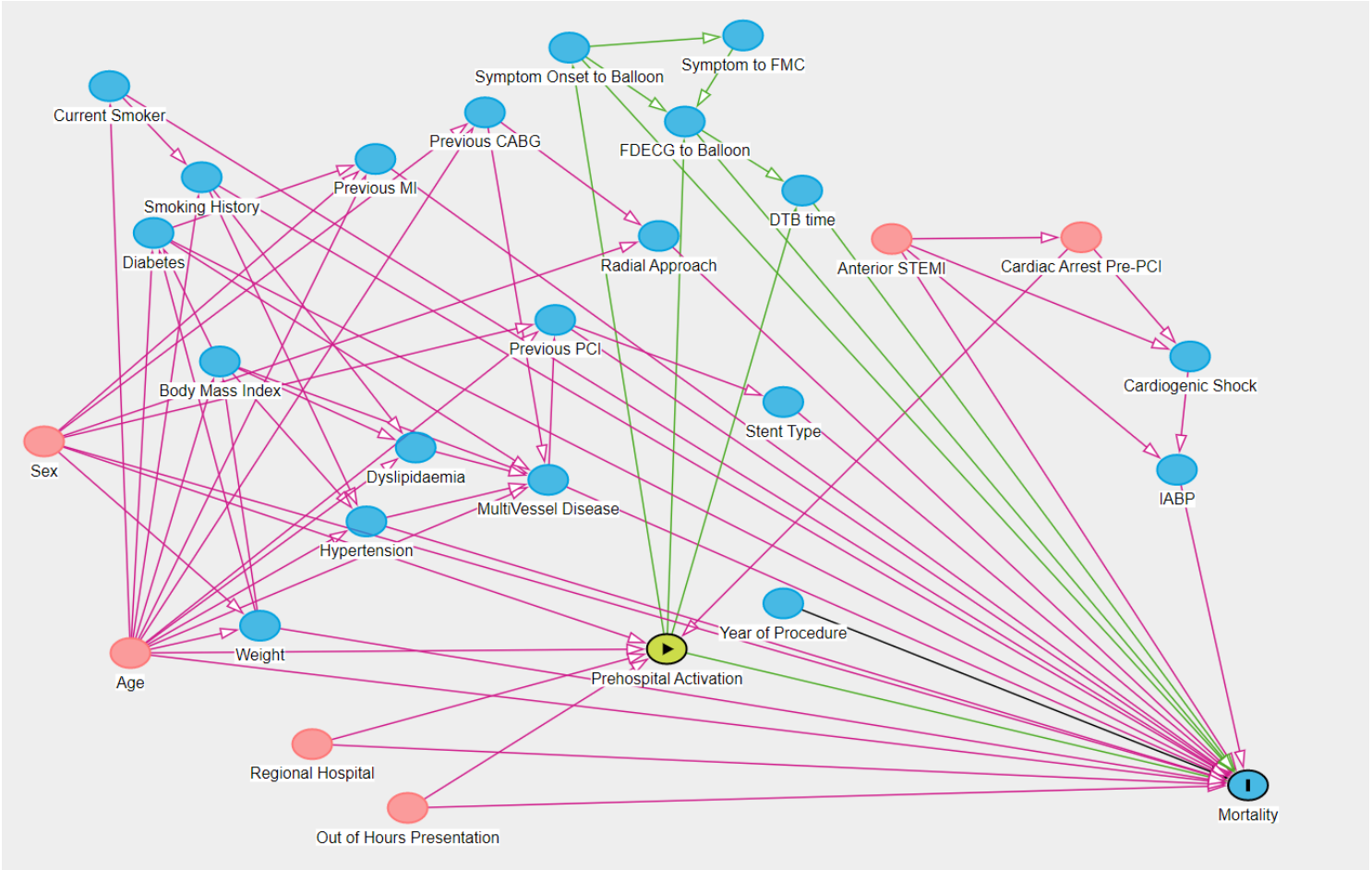
I certify that I have completed the *Autonomous pPCI Referral Checklist* and the patient **has given / has not given** *(circle appropriate response)* consent for the administration of ticagrelor / clopidogrel *(circle appropriate response)* and heparin.

Number		Signature	

Figure S2. Queensland map demonstrating participating primary PCI centres

Queensland map demonstrating Metropolitan centres (TPCH- The Prince Charles Hospital, RBWH – Royal Brisbane and Women's Hospital, PAH – Princess Alexandra Hospital) and Regional centres (CH – Cairns Hospital, TTH – Townsville Hospital, MBH – Mackay Base Hospital, SCUH – Sunshine Coast University Hospital, GCUH – Gold Coast University Hospital)

Figure S3. Dagitty causal pathway diagram



MI – Myocardial Infarction, PCI – Percutaneous Coronary Intervention, CABG – Coronary Artery Bypass Graft, DTB – Door to Balloon, FMC – First Medical Contact, FDECG – First Diagnostic Electrocardiograph, STEMI – ST-segment Elevation Myocardial Infarction, IABP – Intra-aortic Balloon Pump.