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ORIGINAL RESEARCH

Cardiology

Association of pre-hospital time intervals and clinical outcomes in ST-elevation myocardial infarction patients

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Abstract

Study Objectives: Timely coronary reperfusion is critical for favorable outcomes after ST-elevation myocardial infarction (STEMI). A substantial proportion of the total ischemic time is patient related, occurring before first medical contact (FMC). We aimed to expand the limited current understanding of the associations between prehospital intervals and clinical outcomes.

Methods: We conducted a retrospective analysis of consecutive STEMI patients who underwent primary percutaneous coronary intervention (pPCI) (January 2009–March 2016) and assessed the associations between prehospital intervals and the incidence of new heart failure, cardiogenic shock, and hospital length of stay (LOS), adjusting for important clinical variables.

Results: A total of 773 patients (77% men, median age 65 years) met eligibility criteria. The median pre-911 activation interval was 29 minutes (interquartile range: 11, 89); the median 911 call to FMC interval was 12 minutes (interquartile range: 9, 15). In multivariable analysis, there was a V-shaped relationship between the pre-911 activation interval and outcomes: a lower likelihood of new heart failure (odds ratio [OR]

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0.51; 95% confidence interval [CI]: 0.30, 0.87), cardiogenic shock (OR 0.40; 95% CI: 0.21, 0.75) and prolonged LOS (OR 0.24; 95% CI: 0.14, 0.42) for midrange intervals (11–88 minutes) when compared to the early (< 11-minute) interval. There was no statistically significant relationship between total pre-FMC time and FMC to device activation time.

Conclusions: Among ambulance-transported STEMI patients receiving pPCI, the shortest and longest pre-911 activation time intervals were associated with poorer outcomes. However, variation in post-FMC interval alone was not associated with outcomes, suggesting that interventions to reduce pre-FMC intervals must be prioritized.

KEYWORDS
attitudes and practice, emergency medical services, health knowledge, ST-elevation myocardial infarction

1 | INTRODUCTION

1.1 | Background

Timely coronary reperfusion is the cornerstone of ST-elevation myocardial infarction (STEMI) treatment, and primary percutaneous coronary intervention (pPCI), which is available only at selected hospitals, delivered in a timely manner, is the preferred method of reperfusion, as it confers a greater mortality benefit and carries a lower risk of bleeding than fibrinolysis.[1] With reperfusion delays being the primary driver of poor patient outcomes,[2] an integrated STEMI care system aims to achieve the shortest possible time-to-reperfusion from the onset of symptoms[3–5] (no more than 120 minutes from first face-to-face medical contact [FMC] to coronary reperfusion device deployment[5,6]).

Great strides have been made toward minimizing ischemic time by creating regional systems of care that reduce reperfusion times for both fibrinolysis and PCI.[7,8] However, although it is known that prolonged time to reperfusion *after* FMC negatively affects outcomes,[9] little is known about the influence of time intervals occurring *before* FMC. Moreover, a significant proportion of the total ischemic time is patient driven, occurring before FMC: analysis of the international Global Registry of Acute Coronary Events (GRACE) registry showed that the median time from symptom onset to FMC in the United States and Canada was around 2 hours.[10] In a more recent cohort, 66% of patients had a symptom onset to FMC time of greater than 120 minutes.[11] Discouragingly, this interval has not changed over the past 20 years, despite several public health campaigns and other interventions. In addition, time-to-treatment-seeking is disproportionately higher among women and the elderly.[12–14]

1.2 | Importance

A more complete understanding of system and patient factors, as well as outcomes associated with pre-FMC intervals, could inform prehospital interventions initiated by emergency medical services aimed at reducing overall ischemic time and thus improve outcomes among STEMI patients, but our knowledge of these factors is incomplete. Specifically, there remains a limited understanding of the association of the prehospital interval with in-hospital clinical outcomes.

1.3 | Goals of this study

To address this gap, our objectives were as follows:

Primary: (1) To quantify the contribution of prehospital interval to total ischemic time among patients who activate 911, in a modern STEMI system, specifically before FMC; (2) To determine if there are associations between prehospital interval and hospital length of stay (LOS) and the incidence of new heart failure (HF) and cardiogenic shock.

Secondary: To determine if there are associations between relevant patient factors and the pre-911 activation interval.

2 | METHODS

This study received approval from the University of British Columbia Clinical Research Ethics Board (#H19-01535).

2.1 | Design, sample, and data sources

We conducted a retrospective analysis of selected consecutive cases within the Vancouver Coastal Health (VCH) STEMI database, which has been described previously.[8] Briefly, the database captures all STEMI patients who present to any of 13 hospitals within VCH, arriving by any method (directly to a PCI center via ambulance [with or without prehospital ECG] or self-presentation, and those presenting to a community hospital with or without subsequent transfer to a PCI center). Focusing only on patients who were transported by ambulance, we

linked these data to prehospital British Columbia Emergency Health Services (BCEHS) data to identify relevant prehospital time intervals (pre-911 activation and 911 call to FMC). BCEHS, the sole provider of paramedic care in BC, is a multitiered emergency medical services system, responding to patients with fire first-responders, primary care paramedics (PCPs), and advanced care paramedics (ACPs). In locations where ACPs are available, and if the 911 call-taker identifies patients with possible acute coronary syndrome, then both PCP and ACP attend in a layered fashion. However, currently, only ACPs, who comprise less than 10% of all paramedics in the region, are authorized to acquire, interpret, and transmit prehospital ECGs (PHECGs). Thus, if an ACP crew is not quickly available, some suspected ACS patients will not have a PHECG acquired. We included consecutive patients with STEMI (1) from January 2009 to March 2016, (2) in whom STEMI was diagnosed using a PHECG and (3) who were then transported to the hospital via ambulance, and (4) received pPCI. Patients with missing time-interval data were excluded.

2.2 | Measurements

The 3 time intervals of interest were (1) pre-911 activation (although all 911 calls are first routed through a central system that encompasses fire, ambulance, and police, and then forwarded to EHS as appropriate, we use the term "911 activation" for brevity); (2) 911 call to FMC; and (3) FMC to first device deployment. The 2 prehospital time intervals were calculated from the BCEHS database, and the FMC to device time was derived from the VCH STEMI Database. Pre-911 activation was defined as symptom onset to 911 call; further, symptom onset was defined as the patient-reported time that symptoms began, as recorded by the paramedic in their record of care. The time of the 911 call was defined as the time at which the EHS call-taker recorded initial contact by the patient or person calling on behalf of the patient. FMC was defined as the time of the first face-to-face encounter between the EHS paramedic and the patient, as recorded by the paramedic. Device deployment time was defined as the time of first balloon inflation or other device deployment (direct stent or thrombectomy device) during PCI.

2.3 | Outcomes and statistical analysis

The clinical outcomes of interest were (1) new HF; (2) cardiogenic shock; (3) hospital LOS; and (4) mortality, all of which are captured in the VCH STEMI Database, as are baseline clinical characteristics such as age, sex, and preexisting comorbidities. Continuous variables were expressed as medians (interquartile range) or means (±SD), and categorical variables were expressed as percentages. Both pre-911 activation time and 911 to FMC time were initially divided into 4 groups, based on quartiles (Tables S6-S9). The outcome rates were similar among patients in the 2 middle-quartile groups and thus were combined in the main analysis to increase statistical power and interpretability. The resultant 3 time-interval groups were early, midrange, and late, corresponding to times < first quartile, between first and third quartiles, and ≥third quartile. Univariate comparisons of patient characteristics and in-hospital outcomes between time-interval groups were performed using the Kruskal-Wallis test or analysis of variance for continuous variables, and chi-square test or Fisher's exact test for categorical variables, as appropriate. Spearman correlation (rho) was used to assess the association between pre-FMC times and FMC-to-device activation time.

Logistic regression, adjusted for age, sex, and patient characteristics that were associated with time-interval groups ($p < 0.2$ in the univariate comparison), was further used to examine the association between time-interval groups and in-hospital outcomes that were significant in the univariate analysis (HF, in-hospital cardiogenic shock, and hospital LOS greater than 6 days [population mean]). For the LOS analysis, only those who were discharged alive were included in the analysis. Given that in-hospital death was a competing risk for the in-hospital outcomes considered here, we performed a sensitivity analysis to examined the composite outcome of death and each of these in-hospital outcomes.

Patients with missing time-interval data were excluded from the logistic regression analysis. To explore the robustness of our results, we imputed the missing time-interval categories using multiple imputation (100 imputations) with the fully conditional specification method. The imputation model included the adjustment variables used in the main logistic regression analysis, plus patient characteristics which were found to be associated with data missingness, as auxiliary variables.

All data were analyzed with Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, NC).

The Bottom Line

In this study of 773 patients with ST-elevation myocardial infarction presenting to 13 hospitals in Vancouver, Canada, women waited longer before activating 911 compared to men. Both short and longer pre-911 intervals were associated with higher rates of new heart failure, higher rates of cardiogenic shock, and longer length of stay, whereas emergency medical service response times were not linked to worse outcomes.

3 | RESULTS

3.1 | Characteristics of study subjects

There were 2431 patients identified in the VCH STEMI Database during the study time frame, of whom 773 met all study inclusion criteria. (Figure 1). The median age was 65.3 (interquartile range [IQR], 56.7, 75.8) years and 77% were men. An anterior MI was present in 48% of the sample (Table 1).

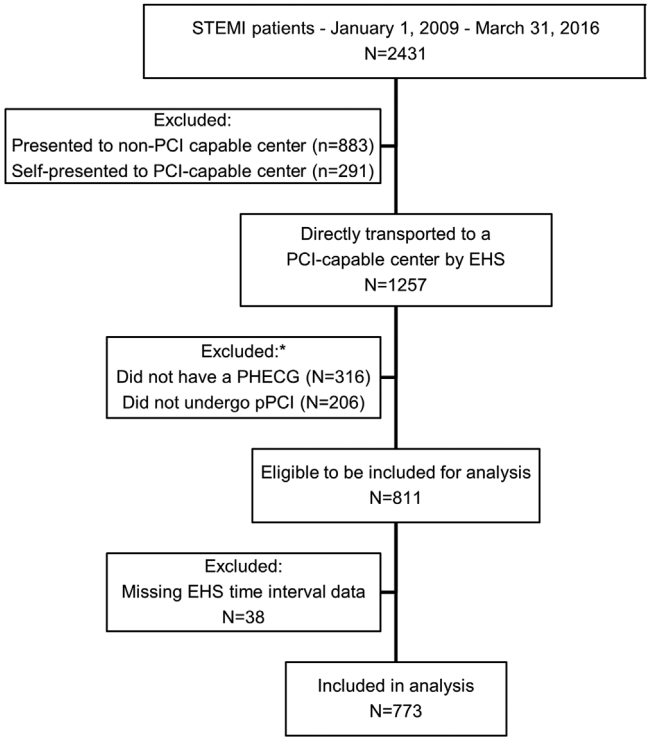

FIGURE 1 Derivation of study sample. Abbreviations: EHS, emergency health services; PHECG, prehospital ECG; PCI, percutaneous coronary intervention; pPCI, primary PCI; STEMI, ST-elevation myocardial infarction.

TABLE 1 Clinical and demographic characteristics

Variable	All ($n = 773$)
Age, years, mean (SD)	66.1 (12.9)
Age, years, median (IQR)	65.3 (56.7, 75.8)
Female sex (%)	178 (23.0)
Current/recent smoker (%)[a]	202 (26.2)
Dyslipidemia (%)[a]	343 (44.5)
Hypertension (%)[a]	413 (53.6)
Diabetes (%)[a]	153 (19.9)
Dialysis (%)[a]	2 (0.3)
Prior myocardial infarction (%)[a]	133 (17.3)
Preexisting heart failure (%)[a]	17 (2.2)
Prior percutaneous coronary intervention (%)[a]	99 (12.9)
Anterior infarction (%)	373 (48.3)
Heart failure on presentation (%)[a]	52 (6.7)
Pre-911 interval, median (IQR)[b]	29.0 (11.0, 89.0)
911 to FMC interval, median (IQR)	12.0 (9.0, 15.0)

[a]Data missing for up to 4 patients.
[b]Data missing for 74 patients.
Abbreviation: IQR, interquartile range.

3.2 | Main results

3.2.1 | Pre-911 activation interval

The overall median symptom onset to 911 interval was 29 minutes (IQR: 11, 89, Table 1), with 50.8% of patients calling within 30 minutes of symptom onset and 31.6% taking 60 minutes or longer.

3.2.2 | 911 Call to FMC Interval

The overall median 911 to FMC interval was 12 minutes (IQR: 9, 15), with 36.9% achieving FMC within 10 minutes, and 75.9% within 15 minutes. The critical STEMI-related intervals are depicted in Figure 2.

3.2.3 | Association of patient characteristics with pre-911 activation interval

Female sex and not having had a prior PCI were significantly associated with longer pre-911 activation interval times (Table 2). No other baseline clinical characteristics were significantly associated with this interval.

3.2.4 | Association of pre-FMC intervals with post-FMC intervals

There was no statistically significant relationship between the total pre-FMC time and FMC to device activation time (rho = -0.01), nor for the subintervals of pre-911 activation (rho = -0.001) or 911 call to FMC (rho = −0.03). There was also no association between pre-FMC time and achievement of the FMC-to-device activation target of 120 minutes (Table S1).

3.2.5 | Association of pre-FMC intervals with clinical outcomes

Univariate analysis (Table 3 and Figure 3) revealed a V-shaped curve of the relationship between the proportion of patients experiencing certain outcomes and the pre-911 interval. Compared to midrange callers (between 11 and 88 minutes), statistically significantly worse outcomes were experienced by both those calling early (< 11 minutes) and those calling late (≥89minutes), (new HF: 23.7% and 24.0% for early and late callers, versus 13.0% for midrange callers; cardiogenic shock: 15.4% and 12.0% for early and late, versus 6.2% for midrange; hospital LOS > 6 days: 27.1% and 19.5% for early and late, versus 9.1% for midrange). No significant associations were observed between 911 call to FMC time and clinical outcomes (Table S2).

In multivariable analysis (Table 4), a similar V-shaped relationship was observed between the pre-911 interval and outcomes. Compared to early callers, those calling in the midrange of time intervals were significantly less likely to have adverse outcomes: new HF (odds ratio [OR]

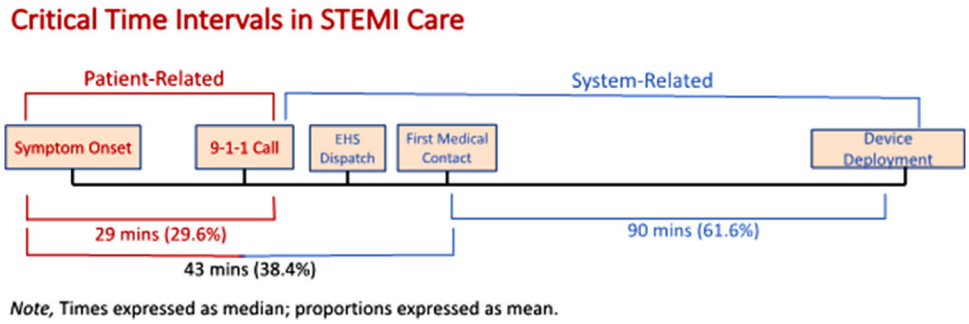

FIGURE 2 Duration and mean proportion of total time of ischemic time subintervals. Abbreviations: EHS, emergency health services; STEMI, ST-elevation myocardial infarction.

TABLE 2 Baseline characteristics, by pre-911 activation interval

Variable	Pre-911 activation interval			*p* value
	Early (< 11 minutes) (*n* = 169)	Midrange (11–88 minutes) (*n* = 355)	Late (≥89minutes) (*n* = 175)	
Age, years				0.244
Mean (SD)	65.6 (12.6)	65.7 (12.9)	67.5 (13.0)	
Median (IQR)	64.2 (56.6, 74.9)	65.0 (56.5, 75.3)	67.1 (56.9, 76.9)	
Range	(38.9, 99.1)	(33.2, 97.7)	(33.4, 96.2)	
Age, *n* (%)				0.704
< 55	37 (21.9)	74 (20.8)	28 (16.0)	
55–64	50 (29.6)	105 (29.6)	47 (26.9)	
65–74	40 (23.7)	86 (24.2)	49 (28.0)	
≥75	42 (24.9)	90 (25.4)	51 (29.1)	
Female sex, *n* (%)	32 (18.9)	81 (22.8)	53 (30.3)	0.040
Current/recent smoker, *n* (%)	37 (22.0)	93 (26.2)	54 (31.0)	0.166
Recent cocaine use, *n* (%)[a]	1 (0.6)	7 (2.0)	5 (2.9)	0.303
Dyslipidemia, *n* (%)	68 (40.7)	166 (46.8)	75 (42.9)	0.389
Hypertension, *n* (%)	85 (50.6)	188 (53.0)	104 (59.4)	0.221
Diabetes, *n* (%)	29 (17.4)	68 (19.2)	41 (23.4)	0.338
Currently on dialysis, *n* (%)	1 (0.6)	0 (0.0)	1 (0.6)	0.240
Prior MI, *n* (%)	35 (21.0)	61 (17.2)	27 (15.4)	0.388
Prior HF, *n* (%)	3 (1.8)	9 (2.5)	4 (2.3)	0.946
Prior PCI, *n* (%)	32 (19.2)	42 (11.8)	16 (9.1)	0.015
Prior CABG, *n* (%)	4 (2.4)	12 (3.4)	2 (1.1)	0.344
Prior TIA/stroke, *n* (%)	9 (5.4)	31 (8.7)	16 (9.1)	0.349
Prior PVD, *n* (%)[a]	7 (4.2)	10 (2.8)	5 (2.9)	0.680
Anterior infarct, *n* (%)	83 (49.1)	184 (51.8)	90 (51.4)	0.839
HF on presentation, *n* (%)	14 (8.3)	16 (4.5)	10 (5.7)	0.223

Note: *p* value based on ANOVA, chi-square test, or Fisher's exact test, as appropriate.
Abbreviations: CABG, coronary artery bypass grafting; HF, heart failure; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TIA, transient ischemic attack.
[a]Data missing for up to 4 patients.

TABLE 3 Clinical outcomes, by pre-911 activation interval

Variable	Pre-911 activation interval			
	Early (< 11 minutes) (*n* = 169)	Midrange (11–88 minutes) (*n* = 355)	Late (≥89minutes) (*n* = 175)	*p* value
Deceased, n (%)	14 (8.3)	14 (3.9)	11 (6.3)	0.116
Postprocedure TIMI flow < 3, n (%)	4/92 (4.3)	15/174 (8.6)	5/89 (5.6)	0.370
In-hospital cardiac arrest, n (%)	16/98 (16.3)	15/186 (8.1)	9/94 (9.6)	0.092
ICH/stroke, n (%)	3 (1.8)	5 (1.4)	4 (2.3)	0.746
In-hospital cardiogenic shock, n (%)	26 (15.4)	22 (6.2)	21 (12.0)	0.002
In-hospital HF, n (%)	40 (23.7)	46 (13.0)	42 (24.0)	0.001
Major bleeding, n (%)	26 (15.4)	38 (10.7)	17 (9.7)	0.197
LVEF closest to discharge[a]				0.071
Median (IQR)	50.0 (39.0, 55.0)	50.0 (40.0, 55.0)	47.0 (40.0, 53.5)	
Mean (SD)	46.3 (12.2)	48.1 (10.9)	45.7 (10.9)	
Range	(10.0, 68.0)	(5.0, 68.0)	(19.0, 67.0)	
LVEF ≤40 (closest to discharge), n (%)[a]	59 (36.4)	100 (28.5)	59 (34.3)	0.145
Hospital length of stay (days)[b]				0.082
Median (IQR)	3.1 (2.6, 6.3)	3.0 (2.5, 4.0)	3.1 (2.5, 5.0)	
Mean (SD)	7.9 (25.4)	4.1 (5.3)	7.5 (29.7)	
Range	(0.5, 306.9)	(1.2, 81.7)	(1.2, 373.2)	
Hospital length of stay > 3 days, n (%)[b]	82 (52.9)	170 (49.9)	95 (57.9)	0.234
Hospital length of stay > 6 days, *n* (%)[b]	42 (27.1)	31 (9.1)	32 (19.5)	<0.001
Hospital length of stay, *n* (%)[b]				<0.001
≤3 days	73 (47.1)	171 (50.1)	69 (42.1)	
4–6 days	40 (25.8)	139 (40.8)	63 (38.4)	
7–9 days	16 (10.3)	12 (3.5)	12 (7.3)	
> 9 days	26 (16.8)	19 (5.6)	20 (12.2)	

Note: *p* value based on Kruskal-Wallis test, chi-square test, or Fisher's exact test, as appropriate.
Abbreviations: ICH, intracranial hemorrhage; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction.
[a]Data missing for 14 patients.
[b]Among those discharge alive.

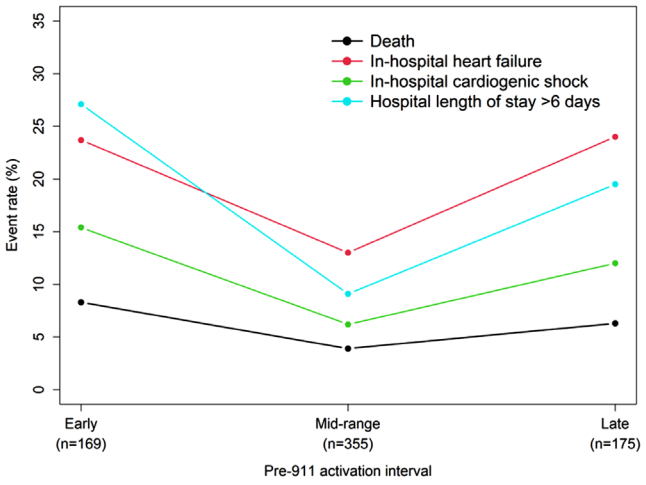

FIGURE 3 Clinical outcomes by pre-911 activation interval

0.51; 95% confidence interval [CI]: 0.30, 0.87); or cardiogenic shock (OR 0.40; 95% CI: 0.21, 0.75) and hospital LOS greater than 6 days (OR 0.24; 95% CI: 0.14, 0.42) but not death. By contrast, no significant differences in outcomes were observed between early and late callers. Older age, anterior infarct, and cardiogenic shock were also independently associated worse outcomes. None of these relationships was observed for the 911-to-FMC interval. Although the pre-911 interval was not associated with mortality, older age, having an anterior infarct and current or recent smoking were (Table S3).

3.2.6 | Sensitivity analysis

Using the composite outcomes of LOS and death, in-hospital HF and death, and cardiogenic shock and death, again, the pre-911 interval was associated with clinical outcomes (midrange intervals predicting better

TABLE 4 Predictors of clinical outcomes

	In-hospital heart failure		In-hospital cardiogenic shock		Hospital length of stay > 6 days	
Variable	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Pre-911 activation interval						
Midrange versus early	0.51 (0.30, 0.87)	0.014	0.40 (0.21, 0.75)	0.005	0.24 (0.14, 0.42)	<0.001
Late versus early	1.09 (0.60, 1.95)	0.782	0.74 (0.37, 1.47)	0.391	0.64 (0.36, 1.13)	0.122
911 call to FMC						
Midrange versus early	0.98 (0.54, 1.77)	0.944	0.96 (0.47, 1.96)	0.913	0.95 (0.52, 1.76)	0.882
Late versus early	0.86 (0.45, 1.65)	0.655	0.86 (0.39, 1.89)	0.710	1.06 (0.55, 2.03)	0.870
Age (per 5-year increase)	1.21 (1.10, 1.33)	<0.001	1.13 (1.00, 1.27)	0.051	1.18 (1.07, 1.30)	0.001
Female sex	1.13 (0.67, 1.93)	0.645	1.51 (0.80, 2.86)	0.203	1.00 (0.58, 1.73)	0.999
Infarct type–anterior	3.18 (1.99, 5.07)	<0.001	1.79 (1.03, 3.09)	0.038	1.18 (0.75, 1.86)	0.463
Current/recent smoker	0.83 (0.47, 1.46)	0.520	1.28 (0.67, 2.43)	0.452	0.45 (0.23, 0.85)	0.015
Recent cocaine use	0.13 (0.00, 3.86)	0.236	2.68 (0.55, 13.14)	0.224	2.76 (0.57, 13.41)	0.207
Hypertension	1.28 (0.79, 2.07)	0.320	0.76 (0.42, 1.38)	0.371	0.97 (0.60, 1.57)	0.901
Prior PCI	0.77 (0.38, 1.56)	0.467	1.20 (0.54, 2.68)	0.651	0.46 (0.21, 1.00)	0.051
Prior TIA/stroke	1.29 (0.62, 2.69)	0.499	1.62 (0.68, 3.82)	0.274	1.46 (0.68, 3.11)	0.334
HF on presentation	16.98 (7.29, 39.55)	<0.001	8.12 (3.89, 16.94)	<0.001	7.25 (2.97, 17.70)	<0.001

Abbreviations: CI, confidence interval; FMC, first medical contact; HF, heart failure; LOS, length of stay; OR, odds ratio; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

outcomes) but not the 911-to-FMC interval. Older age was again associated with in-hospital HF or death, shock, and greater LOS or death, as was anterior infarction and HF on presentation (Table 5).

Among the 811 patients who were eligible, 38 did not have any EHS time-interval data, and 74 did not have pre-911 interval data but had 911-to-FMC-interval data. These 112 patients were excluded from the multivariable analyses, and we noted that there were more patients with HF on presentation within the excluded group. However, the magnitude of the ORs in the analysis using all patients, through multiple imputation of missing data, was similar to the analysis using only patients with complete data (Tables S4 and S5).

3.3 | Limitations

We acknowledge that our work has some limitations. This is a retrospective design, so only association, and not causation, can be concluded. Although there was also no comparison group, we suggest comparison would be difficult in this population. Inclusion of only those whose STEMI was identified by a PHECG acquired by an ACP may have led to selection bias. As described, only ACPs are able to perform PHECG in Vancouver, so dispatchers would preferentially send that type of crew (when available), as opposed to a less skilled primary care crew, if there were features indicating more severe symptoms. It is possible that this potential relationship between PHECG and severity or duration of symptoms confounded associations between timing and clinical outcomes. However, when we compared those who activated EHS but did NOT have a PHECG with those who DID have a PHECG, we found that although the 911 activation to FMC interval was *statistically* significantly longer (1 minute), we suggest that this is not *clinically* significant. Furthermore, the pre-911 activation interval was not significantly different, and most clinical characteristics were similar. Therefore we suggest that overall, our subset of STEMI patients with a PHECG could be generalized to all STEMI patients who activate 911 and are brought to a PCI center. Next, as with most studies, there may have been other variables associated with outcomes that we were not able to measure. Another limitation is the binary nature of our clinical outcomes, as our database does not capture measures of infarction size, such as post-MI ejection fraction or troponin levels. Consistency in measurement of symptom onset is notoriously elusive, in both research and practice,[15–17] but this potential limitation may have been minimized by the fact that all symptom-onset data came from a single EHS system. Our database does not contain longitudinal data beyond hospital discharge and as such, we are unable to explore the impact of prehospital intervals on long-term clinical outcomes. Finally, with large data sets, there is the potential for statistically significant findings that have little clinical relevance, though we believe our findings are important clinically.

4 | DISCUSSION

In a modern cohort of STEMI patients undergoing pPCI, both very short (< 11 minutes) and very long (≥89minutes) pre-911 intervals were significantly associated with new onset of HF, cardiogenic shock, and greater hospital LOS. However, 911 activation to FMC was not associated with any of these outcomes, and FMC to device deployment times generally fell within the recommended guidelines.[5,6] Female sex and

TABLE 5 Sensitivity analysis: Adding death to form composite outcome

	In-hospital heart failure or death		In-hospital cardiogenic shock or death		Hospital length of stay > 6 days or death	
Variable	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Pre-911 activation interval						
Midrange versus early	0.50 (0.29, 0.85)	0.011	0.42 (0.22, 0.78)	0.006	0.27 (0.16, 0.44)	<0.001
Late versus early	1.05 (0.59, 1.87)	0.866	0.75 (0.38, 1.48)	0.408	0.58 (0.34, 0.98)	0.042
911 call to FMC						
Mid-range versus early	0.98 (0.55, 1.75)	0.937	0.94 (0.47, 1.89)	0.865	0.99 (0.57, 1.72)	0.965
Late versus early	0.90 (0.48, 1.71)	0.748	0.84 (0.39, 1.82)	0.664	1.00 (0.55, 1.83)	0.992
Age (per 5-year increase)	1.21 (1.10, 1.34)	<0.001	1.14 (1.02, 1.28)	0.025	1.22 (1.11, 1.34)	<0.001
Female sex	1.06 (0.63, 1.81)	0.819	1.32 (0.71, 2.48)	0.384	1.00 (0.61, 1.64)	0.998
Infarct type–anterior	3.32 (2.09, 5.28)	<0.001	1.85 (1.08, 3.17)	0.025	1.41 (0.93, 2.13)	0.104
Current/recent smoker	1.02 (0.60, 1.76)	0.929	1.42 (0.77, 2.64)	0.263	0.68 (0.39, 1.16)	0.154
Recent cocaine use	0.10 (0.00, 3.10)	0.187	2.28 (0.46, 11.23)	0.310	1.65 (0.34, 8.07)	0.534
Hypertension	1.29 (0.80, 2.08)	0.293	0.83 (0.47, 1.47)	0.524	1.15 (0.74, 1.79)	0.540
Prior PCI	0.87 (0.44, 1.71)	0.685	1.21 (0.56, 2.63)	0.627	0.45 (0.22, 0.91)	0.026
Prior TIA/stroke	1.23 (0.59, 2.57)	0.578	1.47 (0.62, 3.46)	0.379	1.41 (0.71, 2.79)	0.324
HF on presentation	18.29 (7.69, 43.52)	<0.001	8.33 (4.03, 17.24)	<0.001	9.04 (4.15, 19.70)	<0.001

Abbreviations: CI, confidence interval; FMC, first medical contact; HF, heart failure; OR, odds ratio; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

not having had a prior PCI were associated with a longer time to 911 activation, but we found no association between pre-FMC intervals and time to reperfusion, once medical contact was established. Our analysis extends prior literature describing the link between prehospital intervals and clinical outcomes and, to our knowledge, represents the first Canadian report of this association.

In our cohort, the pre-FMC interval comprised about one third of total ischemic time. Encouragingly, our median pre-911 interval of 29 minutes is considerably shorter than times reported in the literature relatively recently, which have ranged from a low of about 1 hour to as much as 3.5 hours.[18–25] This may be because of ongoing improvements in public awareness of the symptoms of MI, although evidence from the United States suggests this remains quite low, and has even declined, among American women, since 2009.[25,26] An alternative explanation is that patients who activate EHS early, may, in fact, have more severe symptoms resulting in prompt treatment seeking. Indeed, the median time for *all* patients arriving by ambulance in our STEMI database (including those who arrived by ambulance but in whom no prehospital ECG was acquired) was similarly short, at 31 minutes, but the median time from symptom onset to arrival at emergency, for self-presenters, was 100 minutes (data not shown). Similarly, as mentioned previously, there were no differences in pre-911 times or other baseline clinical characteristics between those in whom a PHECG was and was not acquired.

Finding no association between the 911 activation to FMC interval and outcomes is likely due to this subinterval being short, suggesting that the system is performing within its practical, logistic limitations. Therefore, we do not view this as a potential target for further shortening symptom onset to reperfusion times.

Our finding of a V-shaped relationship between pre-911 activation intervals and clinical outcomes was somewhat unexpected: patients who called 911 early and late were more likely to develop HF and cardiogenic shock and to require longer hospitalization. This contrasts with findings by Wu et al. who showed that longer, but not shorter pre-FMC times were associated with a higher number of in-hospital complications.[27] However, Wu et al. did not measure the prehospital subintervals discretely, that is, they measured only the symptom-onset-to-hospital-arrival interval. Accordingly, they had fewer interval categories, the shortest being < 1 hour, and thus may have missed associations that occurred with very early callers (eg, < 11 minutes), as observed in our study. Although it is intuitive that a longer pre-911 activation interval would be associated with worse outcomes, our finding of a similar association with a short pre-911 activation interval time is not necessarily intuitive. Indeed, a shorter overall reperfusion time *from first medical contact* has been clearly demonstrated to be associated with improved outcomes among STEMI patients.[1] Again, it is possible that patients who seek help earlier (or for whom others activate 911) do so because of more severe symptoms or signs, which might indicate a larger infarction and, therefore, less potentially salvageable myocardium. However, our study did not show a statistically significant association between longer pre-911 activation intervals and the presence of an anterior versus non-anterior MI, and neither could we find any literature that clearly links symptom severity and myocardial territory involved. Another explanation is that individ-

uals have varied pain tolerance,[28] which may influence time to 911 activation. Thus, this finding is hypothesis generating and warrants further study. Finally, consistent with previous findings[29,30] our analysis also revealed that older age was independently associated with increased rates of new HF, shock, and greater LOS. This may be due to decreased physiological reserve and impaired ability to recover in older patients.

Of note, the interval from symptom onset to 911 accounted for a significant proportion of the total prehospital time (41%), as compared to the small proportion of prehospital time accounted for by the paramedics' very fast response time after the 911 call (15%). This rapid response by paramedics may be a function of including only those with PHECG, because, as previously described, only ACP crews are able to acquire in-field ECGs in the region under study. Dispatch of an ACP crew might have been prompted by either greater symptom severity or shorter duration, or other features suggesting urgency, which, in turn, may have led to shorter paramedic response times. Another factor is the study setting: the city of Vancouver, a highly urban region with very high population density. Thus, paramedic response and transport times may be difficult to reproduce in other settings. Nevertheless, in the prehospital phase, the pre-911 activation interval remains a large contributor to total ischemic time and may be due to patient factors such as lack of MI symptom awareness, denial of symptom significance or symptoms being non-cardiac in nature.[5,14,31,32] Because Vancouver is a major metropolis and there is universal health care in Canada, patients' 911-activation behavior was not likely due to inability to access care. In terms of generalizability, compared to other urban Canadian STEMI cohorts receiving pPCI,[10,14] ours had similar rates of smoking, hypertension, dyslipidemia, and prior cardiac events (Table 1). As such, our cohort is representative of this population.

Importantly, we found no significant relationship between the pre-FMC times and subsequent FMC-to-device times, which suggests that there is equity in the efficiency of the STEMI care system (both pre- and in hospital), once activated. However, in accordance with previous reports, we found that female patients had longer times across both subintervals.[14,33] The longer times in the pre-911 interval could be partially explained by women being more likely to have additional, non-cardiac locations of discomfort.[34–37] The longer times in other subintervals, however, are more challenging to explain and should be the subject of further study.

This study demonstrates that variations in pre-FMC times are associated with clinical outcomes, including HF, cardiogenic shock, and LOS. With respect to longer pre-911 times influencing outcomes, it is discouraging to note that, over the years, multiple public awareness campaigns have sought to raise awareness about the symptoms of MI and the importance of prompt treatment seeking, but with little change in knowledge or treatment-seeking behavior.[18–19,21,23,25] As such, the question remains whether future efforts should refocus on reducing pre-911 activation intervals (which constitute roughly one third of total ischemic time) or on continuing to optimize FMC-to-device times. Prior efforts toward the former have had generally disappointing results, but perhaps innovative approaches, using existing and emerging technologies (eg, smartphone monitoring and alerts), hold promise. The latter focus, however, although under better control than patients 'behavior, may be at or near its optimal performance level.

In conclusion, we have demonstrated an unexpected V-shaped relationship between pre-911 activation times and in-hospital outcomes. This comprehensive time-interval analysis of a modern, optimized STEMI system also confirms that a significant portion of the pre-FMC interval is due to patients' treatment-seeking behavior and provides incremental prognostic information regarding STEMI outcomes. Our findings also extend prior work that women are more likely to have longer treatment-seeking intervals. However, the post-FMC interval was not independently associated with outcomes, suggesting that efforts to develop and test interventions to reduce pre-FMC intervals remain critically important.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Martha H. Mackay and Adam Chruscicki conceived and designed the study. Martha H. Mackay supervised the conduct of the study. Joel Singer and Terry Lee provided statistical advice on study design and Terry Lee analyzed the data. Adam Chruscicki and Martha H. Mackay drafted the manuscript, and all authors contributed substantially to its revision. Martha H. Mackay takes full responsibility for the paper as a whole.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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