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ORIGINAL RESEARCH

Late Outcomes of Patients With Prehospital ST-Segment Elevation and Appropriate Cardiac Catheterization Laboratory Nonactivation

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BACKGROUND: Patients with suspected ST-segment–elevation myocardial infarction (STEMI) and cardiac catheterization laboratory nonactivation (CCL-NA) or cancellation have reportedly similar crude and higher adjusted risks of death compared with those with CCL activation, though reasons for these poor outcomes are not clear. We determined late clinical outcomes among patients with prehospital ECG STEMI criteria who had CCL-NA compared with those who had CCL activation.

METHODS AND RESULTS: We identified consecutive prehospital ECG transmissions between June 2, 2010 to October 6, 2016. Diagnoses according to the Fourth Universal Definition of myocardial infarction (MI), particularly rates of myocardial injury, were adjudicated. The primary outcome was all-cause death. Secondary outcomes included cardiovascular death/MI/stroke and noncardiovascular death. To explore competing risks, cause-specific hazard ratios (HRs) were obtained. Among 1033 included ECG transmissions, there were 569 (55%) CCL activations and 464 (45%) CCL-NAs (1.8% were inappropriate CCL-NAs). In the CCL activation group, adjudicated index diagnoses included MI (n=534, 94%, of which 99.6% were STEMI and 0.4% non-STEMI), acute myocardial injury (n=15, 2.6%), and chronic myocardial injury (n=6, 1.1%). In the CCL-NA group, diagnoses included MI (n=173, 37%, of which 61% were non-STEMI and 39% STEMI), chronic myocardial injury (n=107, 23%), and acute myocardial injury (n=47, 10%). At 2 years, the risk of all-cause death was higher in patients who had CCL-NA compared with CCL activation (23% versus 7.9%, adjusted risk ratio, 1.58, 95% CI, 1.24–2.00), primarily because of an excess in noncardiovascular deaths (adjusted HR, 3.56, 95% CI, 2.07–6.13). There was no significant difference in the adjusted risk for cardiovascular death/MI/stroke between the 2 groups (HR, 1.23, 95% CI, 0.87–1.73).

CONCLUSIONS: CCL-NA was not primarily attributable to missed STEMI, but attributable to "masquerading" with high rates of non-STEMI and myocardial injury. These patients had worse late outcomes than patients who had CCL activation, mainly because of higher rates of noncardiovascular deaths.

Key Words: acute coronary syndrome ■ myocardial injury ■ prehospital ECG interpretation ■ ST-segment–elevation myocardial infarction

Prehospital electrocardiographic identification of ST-segment–elevation myocardial infarction (STEMI) reduces time to reperfusion and improves outcomes either by timely primary percutaneous coronary intervention (PCI) or administration of fibrinolytic therapy (preferably prehospital).[1] While the adoption of prehospital STEMI triage improves reperfusion times, inappropriate cardiac catheterization laboratory (CCL) activations have become a challenging problem, imposing costs on patients, clinicians, and health care

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CLINICAL PERSPECTIVE

What Is New?

- While the adoption of prehospital ST-segment–elevation myocardial infarction triage improves reperfusion times, inappropriate cardiac catheterization laboratory (CCL) activations have become a challenging problem, imposing costs on patients, clinicians, and health care networks.
- Patients who have CCL nonactivation or cancellation have similar crude and higher adjusted risks of death than those who have CCL activation, though reasons for these poor outcomes are not clear.
- CCL nonactivation among patients with paramedic-transmitted ECGs meeting Glasgow algorithm criteria for ST-segment–elevation myocardial infarction was not primarily attributable to missed ST-segment–elevation myocardial infarction, but attributable to "masquerading" with high rates of non–ST-segment–elevation myocardial infarction and myocardial injury.

What Are the Clinical Implications?

- Patients with CCL nonactivation had worse late outcomes than patients who had CCL activation, mainly because of much higher rates of noncardiovascular deaths.
- Irrespective of whether there was CCL activation, there was no significant difference in the adjusted risk of the composite cardiovascular outcome of cardiovascular death/myocardial infarction/stroke between the 2 groups.
- Identifying significant coronary stenoses and/or alternate causes of troponin T elevation in patients who have CCL nonactivation, may lead to identification of remediable causes of risk.

Nonstandard Abbreviations and Acronyms

4th UDMI	Fourth Universal Definition of myocardial infarction
CCL	cardiac catheterization laboratory

networks.[2] Perhaps surprisingly, patients who have CCL nonactivation (also called false-positive STEMI alerts) or cancellation have reportedly similar crude and higher adjusted risks of death than those who have emergency CCL activation.[3,4]

Reported rates of missed STEMI and resultant inappropriate CCL nonactivation have been low in this patient population (1%–3%), so lack of reperfusion is unlikely to have significantly contributed to these poor outcomes.[3,4] However, such patients were generally older and had higher burdens of comorbidities. Also, reports of cardiovascular and noncardiovascular outcomes of this patient population are lacking, and diagnoses have not been adjudicated according to the Fourth Universal Definition of myocardial infarction (4th UDMI).[5] Hence, we adjudicated diagnoses, particularly the frequency of myocardial injury, in patients with prehospital ECGs meeting STEMI criteria, who had emergency CCL activation compared to those who had CCL nonactivation; late clinical outcomes were also determined.

METHODS

Transparency and Openness Promotion

The data that support the findings of this study are available from the corresponding author upon reasonable request. The analysis source code has been made publicly available on Github (https://github.com/akfaour/CCL-NA).

Study Population

We prospectively identified consecutive patients with suspected STEMI who had prehospital ECGs transmitted to interventional cardiologists at a tertiary PCI center (Liverpool Hospital, Sydney, Australia) between June 2, 2010, and October 6, 2016. Patients were included if they were ≥18 years of age and had a transmitted prehospital ECG with a computer diagnosis of STEMI. ECGs were acquired using Lifepak 15 monitors/defibrillators (Physio-Control, Redmond, Washington), and the computer algorithm used was The University of Glasgow algorithm (Glasgow, Scotland). Exclusion criteria were patients with serial or duplicate ECG transmissions, multiple patient encounters (only the first encounter was included), patients who did not have sufficient troponin T testing for adjudication according to the 4th UDMI[5] (troponin not tested or indeterminate myocardial injury pattern), and those with missing data.

The criteria for prehospital ECG acquisition by paramedics included patients with chest pain or equivalent symptoms. A prehospital ECG computer interpretation of STEMI mandated its wireless transmission via Lifenet (Physio-Control) to the hand-held device of the on-call interventional cardiologist. The transmitted ECG contained a paramedic callback number to facilitate discussion of patient presentation and prehospital CCL activation or recommendation of prehospital fibrinolysis if anticipated transport time was prolonged. If the interventional cardiologist agreed with computer interpretation, a single call to the hospital operator activated the CCL team. If the interventional cardiologist disagreed with computer interpretation, or if the prehospital diagnosis of STEMI was unclear or patient candidacy for emergency angiography was questionable, paramedics were instructed to repeat the ECG

and transport the patient to the PCI center for further assessment. The study was approved by the South Western Sydney Local Health District (2019/ETH12962) and the need for informed consent was waived.

Definitions

Prehospital STEMI transmissions that resulted in emergency coronary angiography were classified as CCL activation, and those that did not result in emergency angiography were classified as CCL nonactivation. Patients in whom emergency angiography did not occur due to death were included in the CCL activation group. Fibrinolytic-treated patients who required rescue PCI were included in the CCL activation group, and those with ST-recovery who were scheduled for early angiography were included in the CCL nonactivation group. ECGs were blindly and independently analyzed by 2 interventional cardiologists (A.F. and O.G.). STEMI ECG criteria were defined as ST-segment elevation of ≥1 mm (except ≥2 mm in men >40 years, ≥2.5 mm in men <40 years or ≥1.5 mm in women in leads V2-3) in ≥2 contiguous leads.[5] Posterior myocardial infarction (MI) was defined as ST-segment depression ≥0.5 mm in leads V1-V3 with a prominent R wave or R/S ratio >1.[5] Left main coronary ischemia was defined as ST-segment elevation in lead aVR (augmented vector right) accompanied by ≥1 mm ST-segment depression in ≥6 leads.[5]

The appropriateness of prehospital CCL activations were independently classified by authors (A.F. and O.G.) according to clinical presentation and ECG findings, blinded to the outcome of angiography. Inappropriate CCL nonactivations were defined in patients with all of the following: (1) cardiac ischemic symptoms (<12 hours), (2) STEMI ECG criteria or equivalents, and (3) absence of contraindications to emergency angiography. STEMI equivalents were defined as any of the following: (1) left bundle-branch block (new, presumed new or preexisting with Sgarbossa concordance[6]), (2) posterior MI, (3) left main coronary artery ischemia, and (4) return of spontaneous circulation following witnessed out of hospital cardiac arrest from a shockable rhythm.

Diagnoses were independently adjudicated by authors (A.F. and O.G.) according to the 4th UDMI[5] and classified as (1) MI, (2) acute myocardial injury, (3) chronic myocardial injury, and (4) no myocardial injury. In addition, MI was diagnosed in the presence of (1) symptoms or signs of cardiac ischemia and a single troponin T result >52 ng/L for the fifth-generation assay (Roche Diagnostics, Indianapolis, Indiana)[7] or >0.03 ng/mL for the fourth-generation assay (Roche Diagnostics),[8] and (2) symptoms or signs of cardiac ischemia and death before troponin testing or within 24 hours of a single elevated troponin T result. The fourth-generation troponin T assay was used until June 15, 2011 (99th percentile upper reference limit ≥0.01 ng/mL), and thereafter, the fifth-generation (high sensitivity) troponin T assay (99th percentile upper reference limit ≥14 ng/L). Peak troponin T levels were divided by the upper reference limits to facilitate comparison between fourth-generation and high-sensitivity assays.

Clinical Outcomes

The primary outcome was all-cause death at 2 years. Secondary outcomes included the composite cardiovascular outcome of cardiovascular death/MI/stroke, heart failure hospitalization and noncardiovascular death at 2 years. We also determined the adjusted hazard ratio (HR) for all-cause death and cause-specific HRs for the composite cardiovascular outcome of cardiovascular death/MI/stroke and noncardiovascular death. Follow-up data were obtained from medical records and by contacting cardiologists, general practitioners, patients, or family members. Death was classified as cardiovascular or noncardiovascular by authors (R.P. and J.F.) according to the Academic Research Consortium-2 definitions.[9] Undetermined causes of death were classified as cardiovascular for end point determination as per Academic Research Consortium-2 recommendations. Follow up was obtained until the primary outcome or date of censoring (November 1, 2018).

Statistical Analysis

All analyses were performed using R (v4.1.2, Vienna, Austria) and the *survival* and *cmprsk* packages.[10] Categorical variables are presented as frequency (%) and continuous variables as medians with interquartile range. Pearson Chi-squared or Fisher exact tests were used to compare categorical variables, and the Mann-Whitney *U* test was used for continuous variables. Risk ratios (RR) for the primary and secondary outcomes with 95% CI are presented. Adjusted RR were obtained using a generalized linear model with a log link, Poisson error distribution, and were adjusted for the following clinically relevant covariates: age, sex, diabetes, previous MI, previous stroke, cardiac arrest, bundle branch block (categorized as left bundle-branch block, right bundle-branch block and no bundle-branch block) and troponin T elevation (categorized as troponin T elevation versus no troponin T elevation). These covariates were concurrently forced into the crude models. We produced Kaplan–Meier survival curves stratified by CCL activation. Patients lost to follow up were considered censored.

We used multivariable Cox-regression modeling adjusted for the same covariates to obtain hazard ratios (HR) for all-cause death. To explore competing risks of

the composite cardiovascular outcome of cardiovascular death/MI/stroke and noncardiovascular death, cause-specific HRs were obtained and adjusted for the same covariates. Penalized splines were applied to age to accommodate departures from linearity. We checked for nonproportional hazards graphically and using scaled Schoenfeld residuals.[11] Categorical covariates with time-varying effects were stratified using the *strata* statement within the *coxph* function of the *survival* package. Final models satisfied Cox proportional hazards assumptions. To further explore competing risks, we used the cumulative incidence function to produce cumulative incidence curves. In a prespecified subgroup analysis of patients who had CCL nonactivation, we examined associations between covariates and future risk for all-cause death, the composite cardiovascular outcome of cardiovascular death/MI/stroke, and noncardiovascular death. These models were adjusted for the same covariates as the generalized linear models in addition to the pattern of myocardial injury (instead of troponin T elevation; categorized as MI, myocardial injury and no myocardial injury), to estimate the excess hazard associated with different patterns of myocardial injury. Finally, we performed a post hoc sensitivity analyses to examine the potential confounding effect of inappropriate CCL activations and nonactivations. In this analysis, we compared appropriate CCL nonactivations to appropriate activations.

RESULTS

Of 1583 prehospital ECG transmissions assessed for eligibility, 1033 (65%) met the inclusion criteria and were included in the analysis (Figure 1). Prehospital ECG transmission resulted in 569 (55%) CCL activations and 464 (45%) nonactivations. Three patients in the CCL activation group expired before emergency coronary angiography. Compared with patients who had CCL activation, several baseline clinical characteristics were different among patients with CCL nonactivation, including being older, being more often women, having lower rates of smoking, and family history of coronary artery disease, and higher rates of hypertension, previous MI, and stroke (Table 1). Compared with the study population, patients excluded because of insufficient troponin T results were older and had higher rates of previous stroke and lower rates of family history of coronary artery disease (Table S1).

Among 464 CCL nonactivations, reasons for nonactivation included ST-segment elevation adjudicated as not meeting STEMI ECG criteria (n=111, 24%), artefact because of poor quality ECGs (n=66, 14%), bundle-branch block (n=107, 23%; 57 were right bundle-branch block without STEMI ECG criteria, and 50 were preexisting left bundle-branch block), repolarization abnormality (n=47, 10%), severe comorbid disease, or advanced age (n=26, 5.6%), absence of cardiac ischemic symptoms (n=25, 5.4%), transient ST-segment elevation (n=20, 4.3%), inappropriate CCL nonactivation (n=19, 4.1% of nonactivations; 1.8% of prehospital ECG transmissions), and others (n=43, 9.6%; Table S2). In the CCL nonactivation group (n=464), 125 (27%) patients had adjudicated ECG criteria for STEMI on the index ECG, though 57 (12%) of these patients did not have an adjudicated index diagnosis of STEMI. Diagnoses in the latter group (n=57), included repolarization abnormalities (n=21, 37%), transient (<20 min) rather than persistent ST-segment elevation (n=20, 35%), pericarditis (n=14, 25%), and others (n=2, 3%) (Table S3).

Among 569 patients who had CCL activation, the adjudicated index diagnoses included MI (n=534, 94%, of which 99.6% were STEMI and 0.4% non-STEMI), acute myocardial injury (n=15, 2.6%), no myocardial injury (n=14, 2.5%), and chronic myocardial injury (n=6, 1.1%) (Figure 1 and Table 1). In the CCL nonactivation group (n=464), the diagnoses included MI (n=173, 37%, of which 61% were non-STEMI and 39% STEMI), no myocardial injury (n=137, 30%), chronic myocardial injury (n=107, 23%), and acute myocardial injury (n=47, 10%). PCI was performed in 89% (n=509) of patients who had CCL activation (n=569) (Table 1). Among 464 patients who had CCL nonactivation, nonemergent invasive coronary angiography was performed in 114 (25%) patients, and 53 (11%) underwent PCI during the index hospitalization.

Clinical Outcomes

Over a median follow-up of 3.1 years [interquartile range, 2.1–4.3] (3304 person-years), death from any cause occurred in 227 patients (22%), and 45 (4.4%) were lost to follow-up. Patients who had CCL nonactivation compared with CCL activation had a higher crude risk of all-cause death at 2 years (23% versus 7.9%; RR, 2.94; 95% CI, 2.13–4.08) (Table 2 and Figure 2). After adjusting for covariates, the RR was 1.58, 95% CI, 1.24–2.00.

The proportion of deaths from cardiovascular and noncardiovascular causes at 2 years differed between the 2 groups (Figure 3). The crude risk of cardiovascular death was higher in patients who had CCL nonactivation than those who had CCL activation (12% versus 6.2%; RR, 2.03; 95% CI, 1.36–3.04) (Table 2). After adjustment, the RR was 1.33, 95% CI, 0.99–1.76. Patients who had CCL nonactivation compared with CCL activation had a higher crude risk of the composite cardiovascular outcome of cardiovascular death/MI/stroke at 2 years (18% versus 13%; RR, 1.34; 95% CI, 1.01–1.79), and following adjustment for covariates, the

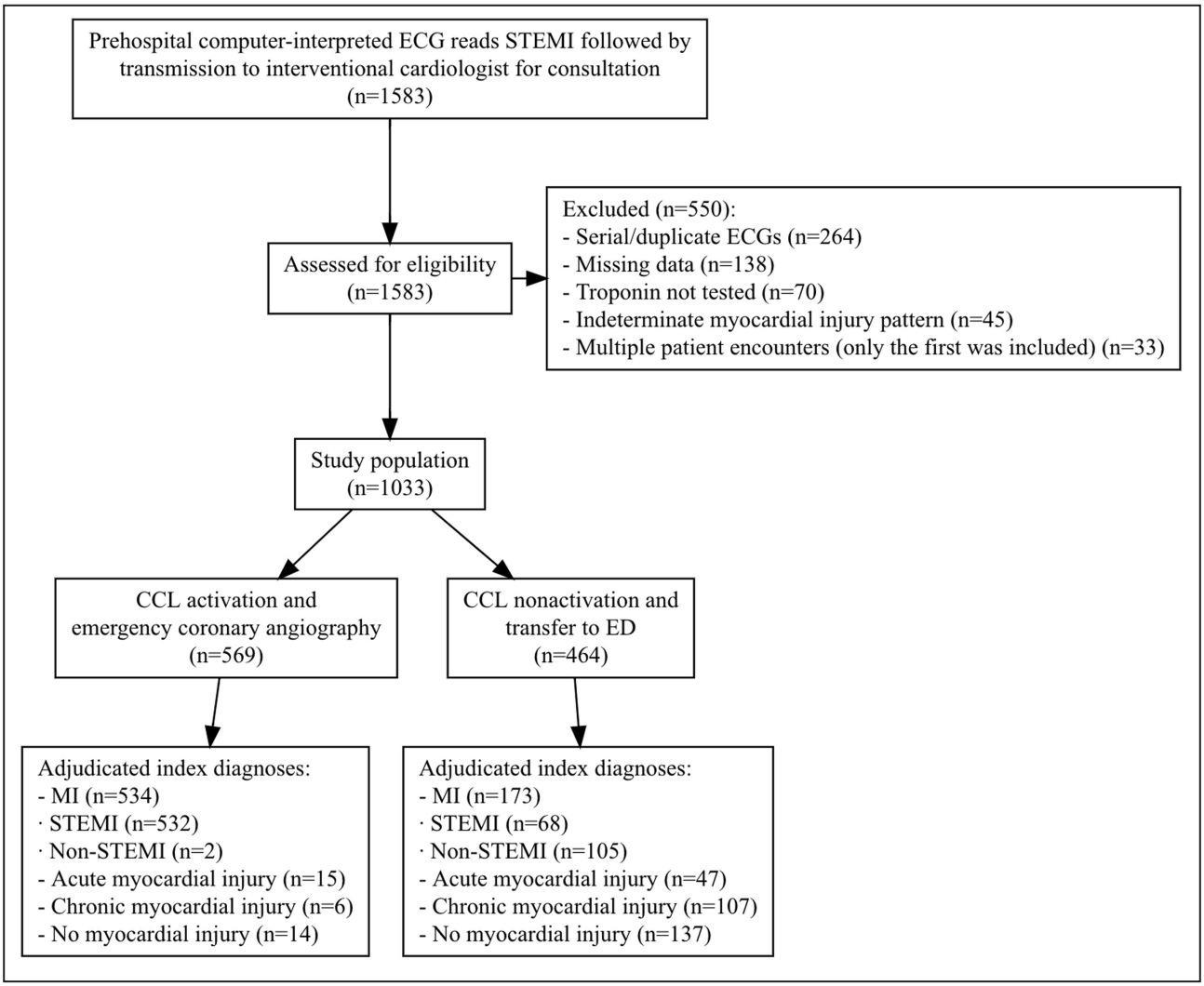

Figure 1. Study flow diagram with identification of the study population by classification according to cardiac catheterization laboratory activation and the Fourth Universal Definition of Myocardial Infarction.
Three patients with CCL activation expired before emergency coronary angiography. Missing data was due to insufficient identifying patient information on the transmitted ECG to link to a particular patient and/or procedure. CCL indicates cardiac catheterization laboratory; ED, emergency department; MI, myocardial infarction; and STEMI, ST-segment elevation myocardial infarction.

RR was 1.18, 95% CI, 0.91–1.50 (Table 2 and Figure 4). The risk of late noncardiovascular death was 11% in patients who had CCL nonactivation compared with 1.8% in those who had CCL activation (unadjusted RR, 6.13; 95% CI, 3.14–11.96 and adjusted RR, 1.61; 95% CI, 1.17–2.18). There were no significant differences in the 2-year crude and adjusted RRs of MI and stroke between the 2 groups.

CCL nonactivation was associated with an increase in the adjusted HR for all-cause death (HR, 2.26; 95% CI, 1.61–3.17) (Table 3). Following adjustment for covariates, the cause-specific HR for the composite cardiovascular outcome of cardiovascular death/MI/stroke (with noncardiovascular death as the competing outcome) was 1.23, 95% CI, 0.87–1.73. Patients in the CCL nonactivation group had an increased adjusted cause-specific HR for noncardiovascular death (3.56; 95% CI, 2.07–6.13). Patients who had CCL nonactivation compared with CCL activation had higher crude and adjusted risks of heart failure hospitalization at 2 years (11% versus 2.1%; unadjusted RR, 5.01; 95% CI, 2.70–9.30 and adjusted RR, 1.49; 95% CI, 1.06–2.05).

Predictors of Adverse Outcomes in Patients With CCL Nonactivation

In patients who had CCL nonactivation, left or right bundle-branch block on the index ECG and a diagnosis of MI or myocardial injury on index presentation were independent predictors of all-cause death (Table 4). A history of previous stroke and a diagnosis of MI on index presentation were independent predictors of the composite cardiovascular outcome of

Table 1. Baseline Characteristics Stratified by CCL Activation

Variable	CCL Activation (n=569)	CCL Nonactivation (n=464)	*P* value
Baseline characteristics			
Age, y	62 [53–72]	71 [58–80]	<0.001
Female	135 (24)	150 (32)	0.002
Medical history			
Diabetes	159 (28)	154 (33)	0.068
Hypertension	337 (59)	321 (69)	<0.001
Dyslipidemia	340 (60)	266 (57)	0.43
Previous MI	108 (19)	156 (34)	<0.001
Previous stroke	34 (6.0)	55 (12)	<0.001
Family history of CAD	67 (12)	37 (8.0)	0.043
Smoker	313 (55)	204 (44)	<0.001
Adjudicated index ECG			
STEMI ECG Criteria	550 (97)	125 (27)	<0.001
Nondiagnostic ST-segment elevation	12 (2.1)	118 (25)	<0.001
Q waves	177 (31)	76 (16)	<0.001
Left bundle-branch block	9 (1.6)	54 (12)	<0.001
Right bundle-branch block	25 (4.4)	79 (17)	<0.001
Left ventricular hypertrophy	70 (12)	79 (17)	0.032
Presentation characteristics			
Cardiac arrest	12 (2.1)	5 (1.1)	0.19
Peak troponin T/upper reference limit*	238 [77–482]	3 [1–33]	<0.001
Fibrinolytic therapy	18 (3.2)	10 (2.2)	0.32
Invasive coronary angiography	566 (99)	114 (25)	<0.001
Culprit coronary artery	529 (93)	87 (19)	<0.001
PCI	509 (89)	53 (11)	<0.001
CABG	7 (1.2)	6 (1.3)	0.93
Adjudicated index diagnoses†			
MI	534 (94)	173 (37)	<0.001
STEMI	532 (93)	68 (15)	<0.001
Non-STEMI	2 (0.4)	105 (23)	<0.001
Acute myocardial injury	15 (2.6)	47 (10)	<0.001
Chronic myocardial injury	6 (1.1)	107 (23)	<0.001
No myocardial injury	14 (2.5)	137 (30)	<0.001

Values are n (%) or median [interquartile range]. Three patients with CCL activation expired before emergency coronary angiography. CABG indicates coronary artery bypass graft surgery; CAD, coronary artery disease; CCL, cardiac catheterization laboratory; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

*Peak troponin T levels were divided by the upper reference limits to facilitate comparison of results between fourth-generation and high-sensitivity assays.

†Adjudicated according to the Fourth Universal Definition of MI.

cardiovascular death/MI/stroke. Right bundle-branch block on the index ECG and a diagnosis of myocardial injury on index presentation were independent predictors of noncardiovascular death.

Sensitivity Analysis

The results of the sensitivity analysis, in which we compared appropriate CCL nonactivations (n=445) to appropriate CCL activations (n=555), were similar to the primary analysis (Table S4).

DISCUSSION

In our cohort of consecutive prehospital ECG transmissions meeting STEMI criteria, after interventional cardiologist over-read, CCL nonactivation (emergently) was inappropriate in only 1.8%. However, approximately one third of patients with CCL nonactivation had MI (largely non-STEMI), and one third had myocardial injury. Of patients who had CCL nonactivation, about one quarter did not survive 2 years. Their crude mortality rate was ≈3 times that of patients who had CCL activation, predominantly attributable to more noncardiovascular deaths. In patients who had CCL nonactivation, right bundle-branch block and myocardial injury were the strongest predictors of all-cause and noncardiovascular death. After considering the competing risk of noncardiovascular death and adjusting for covariates, the risk of the key composite cardiovascular outcome of cardiovascular death/MI/stroke was similar.

Inappropriate CCL activations are ubiquitous in clinical practice,[4,12–22] and impose costs on patients, clinicians, and health care networks.[2] Reported rates vary widely and range between 1% and 65%.[4,12–22] This heterogeneity occurs for various reasons, including the source of CCL activation, study definitions, and system characteristics of health care delivery. Rates of inappropriate CCL activations are often reported,[4,12–22] with outcome comparisons usually between STEMI true-positive and false-positive diagnoses.[12,18,19] Only 2 studies report on the clinical outcomes of CCL nonactivation or cancellation[3,4] and to our knowledge, ours is the first report of late cardiovascular outcomes considering the competing risk of noncardiovascular death, which was the predominant cause of unadjusted late mortality. We also report high rates of non-STEMI and myocardial injury in these patients who met ECG criteria for STEMI but had CCL nonactivation. Prior studies reported similar crude and higher adjusted risks of all-cause death in patients with CCL nonactivation or cancellation relative to those with CCL activation.[3,4] Thus, given their vulnerability, these patients should be triaged to tertiary centers.[3,4]

Table 2. Clinical Outcomes at Two Years Stratified by CCL Nonactivation Versus Activation

Variable	CCL Activation (n=569)	CCL Nonactivation (n=464)	CCL Nonactivation versus activation	
			Unadjusted RR (95% CI)	Adjusted RR (95% CI)
All-cause death*	45 (7.9)	108 (23)	2.94 (2.13–4.08)	1.58 (1.24–2.00)
Cardiovascular death/MI/stroke†	75 (13)	82 (18)	1.34 (1.01–1.79)	1.18 (0.91–1.50)
Cardiovascular death	35 (6.2)	58 (12)	2.03 (1.36–3.04)	1.33 (0.99–1.76)
MI	36 (6.3)	23 (5.0)	0.78 (0.47–1.30)	0.89 (0.57–1.34)
Stroke	11 (1.9)	12 (2.6)	1.34 (0.60–3.00)	1.18 (0.62–2.02)
Noncardiovascular death	10 (1.8)	50 (11)	6.13 (3.14–11.96)	1.61 (1.17–2.18)
Heart failure hospitalization	12 (2.1)	49 (11)	5.01 (2.70–9.30)	1.49 (1.06–2.05)

Values are n (%) with RR (95% CI). Adjusted RR were obtained using a generalized linear model with a log link, Poisson error distribution, and adjusted for age, sex, diabetes, previous MI, previous stroke, cardiac arrest, bundle branch block, and troponin elevation. CCL indicates cardiac catheterization laboratory; MI, myocardial infarction; and RR, risk ratio.

*Causes of death were undetermined in 30 patients and were classified as cardiovascular.

†A composite outcome of cardiovascular death/MI/stroke.

In our cohort of patients who had CCL nonactivation, 37% had MI as their adjudicated diagnosis, of whom 61% had a non-STEMI, similar to previous reports.[3,4] Ducas and colleagues reported 380 computer-assisted paramedic CCL activations with remote physician over-read, a CCL nonactivation rate of 41%, of which 44% had a final diagnosis of acute coronary syndrome.[3] In 2018, Lange and colleagues reported 1332 consecutive CCL activations involving a combination of computer-assisted paramedic and emergency physician-initiated CCL activations. The CCL cancellation rate was 65%, of which 21% of patients had elevated cardiac biomarkers.[4] To qualify for MI peak troponin T levels >0.78 ng/mL were needed, much higher than if MI had been adjudicated according to the 4th UDMI, probably resulting in an underestimation of the MI rate; myocardial injury rates were not reported.[4] As well as a higher MI rate adjudicated according to the 4th UDMI, one third of CCL nonactivation patients had acute or chronic myocardial injury.

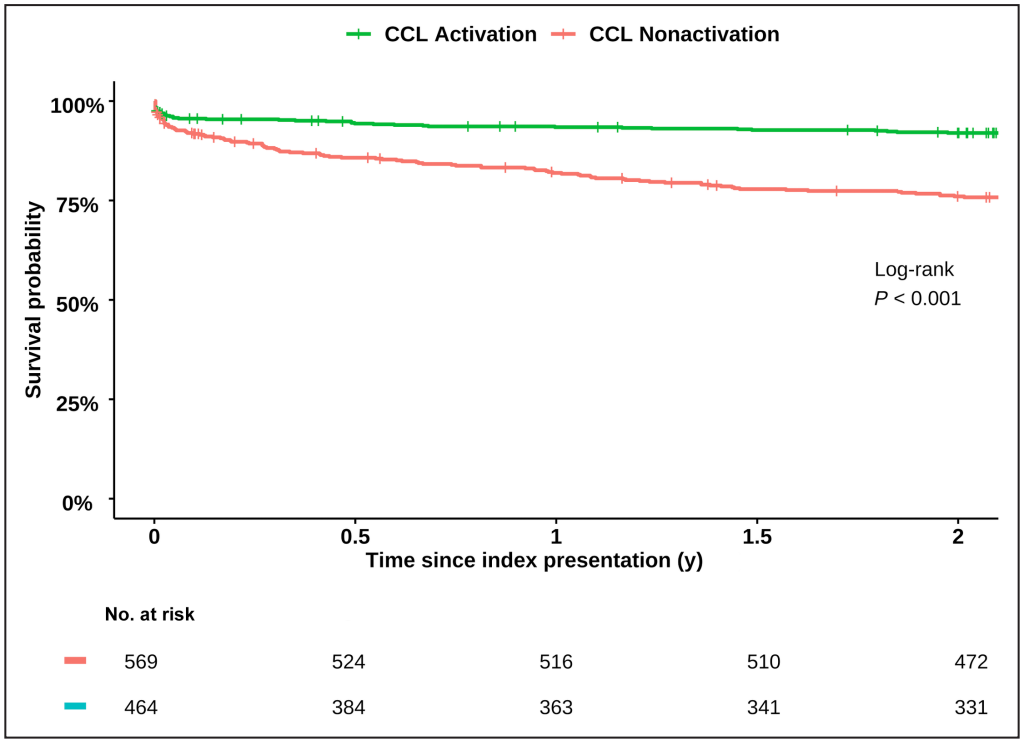

Figure 2. Kaplan–Meier curves illustrating the risk of death from any cause through to 2 years stratified by CCL activation versus nonactivation, with table of number at risk.
Comparison of groups was obtained using the log-rank test. CCL indicates cardiac catheterization laboratory.

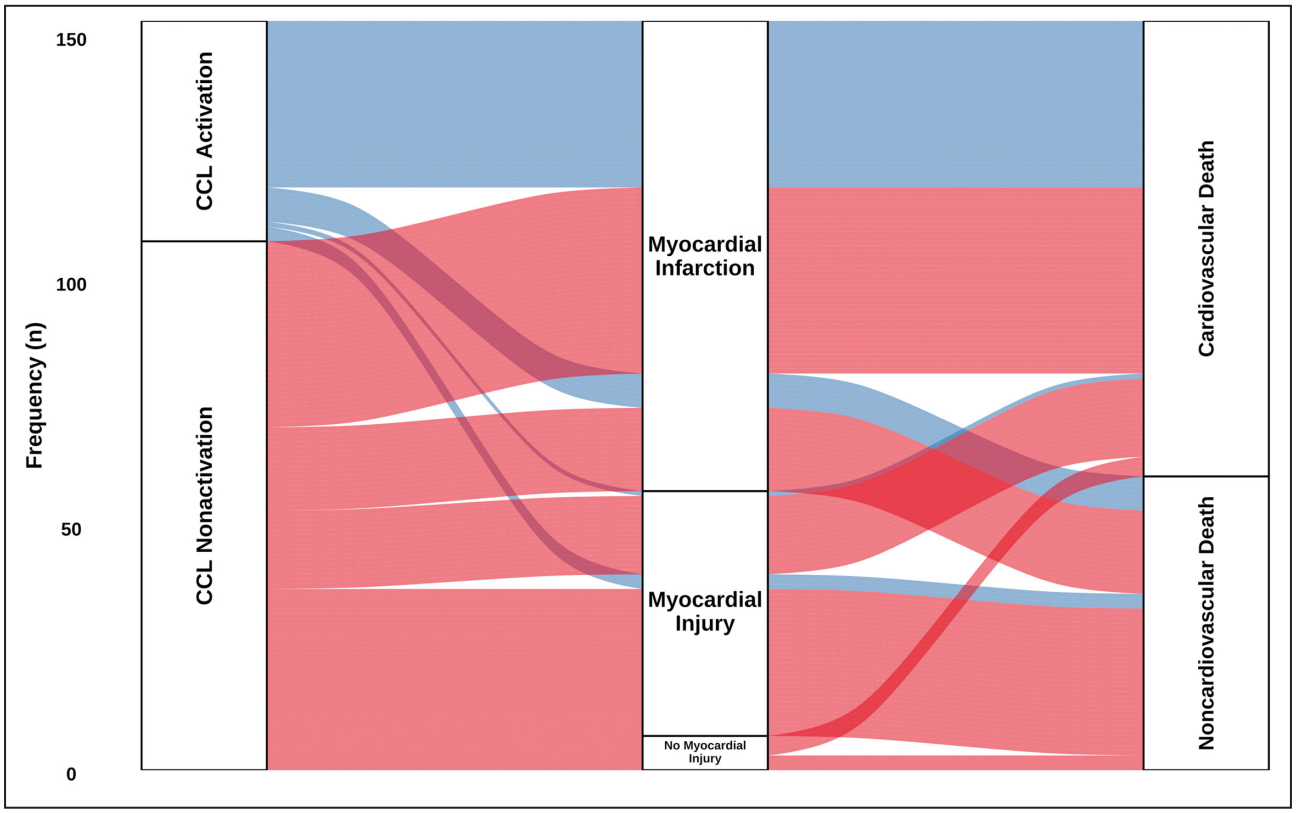

Figure 3. Alluvial plot illustrating the frequency of cause of death at 2 years grouped by CCL activation and adjudicated index diagnosis.
CCL activation (blue) and CCL nonactivation (red). The width of the band indicates the relative size of the population. CCL indicates cardiac catheterization laboratory.

Myocardial injury is common in clinical practice accounting for between 31% and 73% of all elevations in cardiac troponin in patients presenting with suspected acute coronary syndrome.[23–32]

We observed increased adjusted risks of all-cause death in patients who had CCL nonactivation compared with emergency CCL activation, with differences primarily due to higher rates of noncardiovascular deaths. While our findings are broadly consistent with those of Lange and colleagues,[4] our adjusted analyses clarify that these outcomes cannot be explained by advanced age and high burdens of comorbidities. We considered the possibility of bias due to confounding by inappropriate CCL activations and nonactivations, and our sensitivity analyses confirmed the robustness of the findings of the primary analysis.

Although the risk of late mortality in patients who had CCL nonactivation was largely because of an increased risk of noncardiovascular death, the rate of cardiovascular death/MI/stroke was 18%, and 12% had cardiovascular death. While CCL nonactivation patients had higher 2-year crude risks of cardiovascular death and cardiovascular death/MI/stroke than those who had CCL activation, after considering the competing risk of noncardiovascular death and adjusting for clinically relevant covariates, risks of cardiovascular death/MI/stroke were not different. Our findings contrast with those reported by Lange and colleagues, who showed a lower crude risk of cardiovascular death at 2 years in patients who had CCL cancellation compared to those who had CCL activation (3.0% versus 11.8%; $P<0.001$), suggesting differences in patient populations undergoing prehospital ECG transmission for suspected STEMI.[4] Our higher MI rate (37%) in our cohort of CCL nonactivation patients may in part represent our adjudication process.

Adjudicated myocardial injury on index presentation was one of the strongest predictors of all-cause and noncardiovascular death in patients who had CCL nonactivation. Several studies report an increased risk of all-cause and noncardiovascular death in unselected patients presenting with myocardial injury.[25,29,31,32] In an analysis of hospitalized patients, Chapman and colleagues found that a diagnosis of myocardial injury or type 2 MI relative to type 1 MI was associated with an increased risk of noncardiovascular death at 2 years.[25] A large retrospective analysis of 9800 patients with myocardial injury from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated

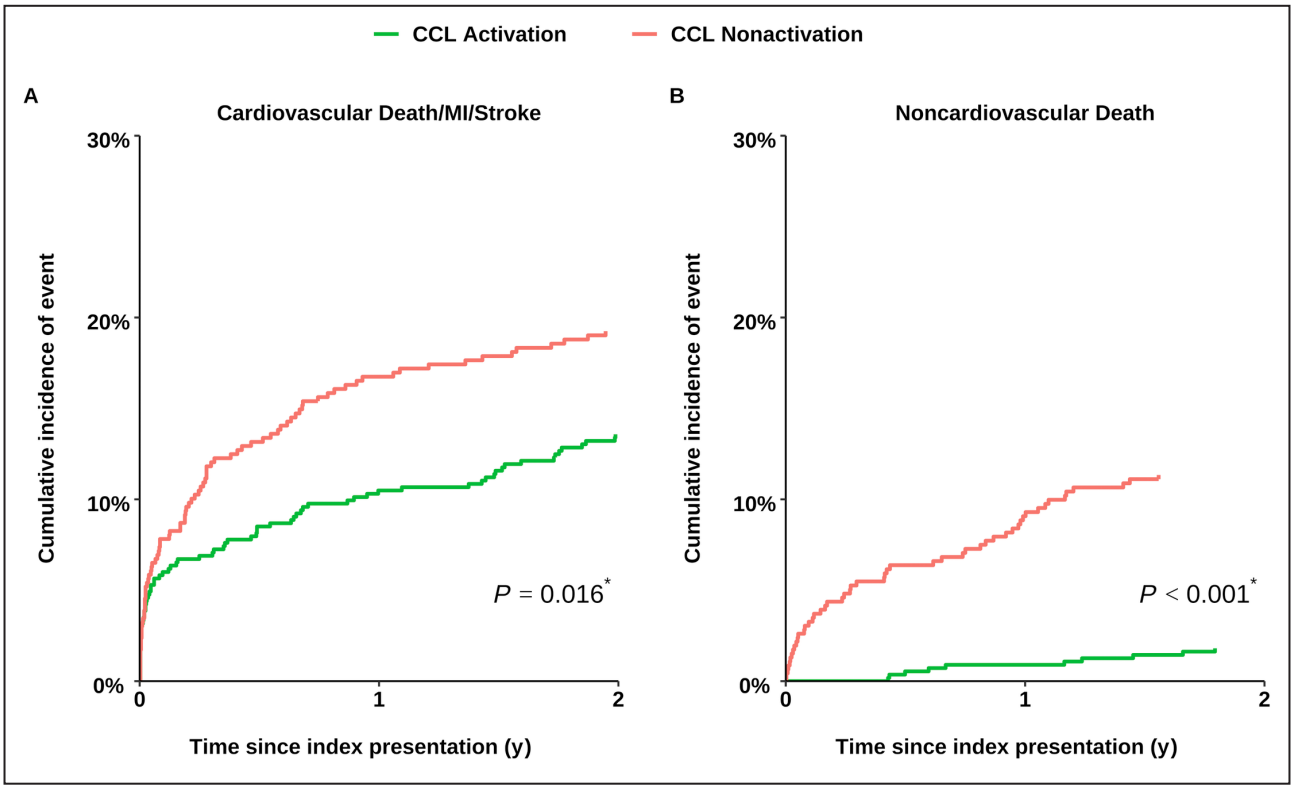

Figure 4. Cumulative incidence curves illustrating risk of the composite outcome of cardiovascular death/MI/stroke (A), and competing risk of noncardiovascular death (B) through to 2 years in patients with CCL activation vs nonactivation.
CCL indicates cardiac catheterization laboratory; and MI, myocardial infarction. *Comparison of groups was obtained using Gray test.

According to Recommended Therapies) registry found higher risks of noncardiovascular death compared to patients without troponin elevation.[29] Similarly, in the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome) trial, which evaluated the implementation of a high-sensitivity troponin assay in patients with suspected acute coronary syndrome, the risk of noncardiovascular death was highest in patients with myocardial injury.[31] In contrast, in an observational cohort of 22 589 patients presenting with suspected acute coronary syndrome, Kadesjo and colleagues found a lower adjusted risk of noncardiovascular death in patients with myocardial injury compared to those with no myocardial injury,[30] though competing risks were not reported, so cardiovascular deaths may have reduced the proportion of patients at risk of noncardiovascular death.

The applicability of our findings to other systems of STEMI care may in part depend on the diagnostic accuracy of the Glasgow computer ECG algorithm for prehospital STEMI identification. Rule-based computer ECG algorithms have similar diagnostic accuracy, and the results of studies examining the diagnostic accuracy of the Glasgow algorithm are shown in Table S5, and Table S6 compares this with the Marquette-12SL algorithm (GE Healthcare, Chicago, Illinois). Computer algorithms using a combination of ST-segment elevation and other ECG markers of acute coronary occlusion (such as hyperacute T waves, de Winter pattern, QRS proportionality, terminal QRS distortion and the South African flag sign)[33] would identify a greater number of patients with acute coronary occlusion. Furthermore, studies using machine learning algorithms report high sensitivity (≥96%) and specificity (≥97%) for detecting STEMI, though these algorithms have not been tested in the prehospital setting and are not in widespread clinical use.[34,35] Also, the positive predictive value and negative predictive value of the Glasgow algorithm depends on the baseline likelihood of STEMI in the particular study population. As our STEMI system of care used prehospital computer interpretation with remote interventional cardiologist over-read, we would expect where there is a lower likelihood of STEMI a larger proportion of patients would have CCL nonactivation and the opposite would occur when there is a higher likelihood of STEMI.

Limitations

Our study has several important limitations. First, this was a single center study with prehospital ECG interpretation using the Glasgow algorithm for STEMI and

Table 3. HR for All-Cause Death and Cause-Specific HRs for the Composite Outcome of Cardiovascular Death/MI/Stroke and Noncardiovascular Death in Patients With CCL Nonactivation Versus Activation in Unadjusted and Adjusted Cox-Regression Models

Variable	HR (95% CI)	*P* value
All-cause death		
Model 1*	3.32 (2.45–4.49)	<0.001
Model 2†	2.31 (1.69–3.15)	<0.001
Model 3‡	2.26 (1.61–3.17)	<0.001
Cardiovascular death/MI/stroke§,‖		
Model 1*	1.52 (1.14–2.02)	0.004
Model 2†	1.18 (0.87–1.58)	0.29
Model 3‡	1.23 (0.87–1.73)	0.24
Noncardiovascular death§		
Model 1*	5.30 (3.23–8.68)	<0.001
Model 2†	3.49 (2.11–5.79)	<0.001
Model 3‡	3.56 (2.07–6.13)	<0.001

Multivariable Cox-regression with CCL activation as the referent group. Stratification was applied to history of previous MI, stroke, cardiac arrest, and troponin T elevation to accommodate nonproportional hazards. *P*-value for inclusion of index diagnosis term. CCL indicates cardiac catheterization laboratory; HR, hazard ratio; and MI, myocardial infarction.

*Unadjusted.

†Adjusted for age and sex.

‡As per model 2, with adjustment for diabetes, previous MI, previous stroke, cardiac arrest, bundle branch block, and troponin elevation.

§Cause-specific multivariable Cox-regression.

‖A composite outcome of cardiovascular death/MI/stroke.

remote interventional cardiologist consultation, which may limit the broader applicability of our findings to other care processes. Second, while every effort was made to minimize misclassification bias by independent adjudication of myocardial injury by 2 cardiologists, this may still have occurred, particularly as there were challenges in differentiating between type 2 MI and acute myocardial injury. Third, while our risk stratification models were adjusted for clinical covariates, residual confounders may still be unaccounted for, including treatment variations or illness severity. Finally, our findings are hypothesis-generating, and causality cannot be inferred because of the study's observational nature.

CONCLUSIONS

In patients meeting STEMI ECG criteria, CCL nonactivation was rarely inappropriate or attributable to missed STEMI. Among these patients, rates of MI and myocardial injury were high. Patients in the CCL nonactivation group died more frequently than those who had CCL activation, primarily because of an excess of noncardiovascular deaths. Cardiovascular event rates were also high among this population, though there was no significant difference in the adjusted risk of cardiovascular death/MI/stroke between the 2 groups. In patients who had CCL nonactivation, right bundle-branch block and myocardial injury were the strongest predictors of all-cause and noncardiovascular death. Identifying significant coronary stenoses and/or alternate causes of troponin T elevation in patients who have CCL nonactivation, may lead to identification of remediable causes of risk.

Table 4. HR for All-Cause Death and Cause-Specific HRs for the Composite Outcome of Cardiovascular Death/MI/Stroke and Noncardiovascular Death in Patients With Cardiac Catheterization Laboratory Nonactivation Alone in Adjusted Cox-Regression Models

Variable	All-cause death		Cardiovascular Death/MI/Stroke*		Noncardiovascular death	
	HR (95% CI)	*P* value	HR (95% CI)†	*P* value	HR (95% CI)†	*P* value
Female sex	1.14 (0.79–1.64)	0.47	1.00 (0.64–1.57)	>0.99	1.22 (0.73–2.04)	0.44
Diabetes	1.09 (0.76–1.57)	0.65	1.51 (0.98–2.33)	0.065	0.77 (0.46–1.30)	0.34
Previous MI	1.02 (0.72–1.45)	0.90	1.02 (0.67–1.56)	0.92	1.02 (0.62–1.68)	0.93
Previous stroke	1.27 (0.82–1.97)	0.28	1.72 (1.02–2.90)	0.042	1.37 (0.75–2.53)	0.31
Bundle branch block‡						
No bundle branch block	…		…		…	
Left bundle-branch block	1.65 (1.05–2.61)	0.032	1.68 (0.96–2.94)	0.069	1.90 (0.99–3.66)	0.054
Right bundle-branch block	1.78 (1.17–2.71)	0.007	1.18 (0.67–2.08)	0.57	2.17 (1.24–3.79)	0.006
Myocardial injury pattern§						
No myocardial injury	…		…		…	
Myocardial injury	2.27 (1.27–4.06)	0.006	1.25 (0.59–2.66)	0.57	3.35 (1.52–7.40)	0.003
MI	2.58 (1.46–4.56)	0.001	4.07 (2.07–7.99)	<0.001	2.06 (0.90–4.72)	0.088

Multivariable Cox-regression. Penalized splines were applied to age to accommodate nonlinearity and stratification was applied to cardiac arrest to accommodate nonproportional hazards. HR indicates hazard ratio; and MI, myocardial infarction.

*A composite outcome of cardiovascular death/MI/stroke.

†Cause-specific multivariable Cox-regression.

‡Patients without bundle branch block as the referent group.

§Patients without myocardial injury as the referent group.

ARTICLE INFORMATION

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Supplemental Material

Tables S1-S6
References 36–45

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Characteristics of the Study Population with Patients Excluded Because of Insufficient Troponin T Results

Variable	**Study Population** (n=1033)	**Excluded** (n=115)	**P-value**
Baseline characteristics			
Age, years	65 [54-77]	73 [62-84]	<0.001
Female	285 (28)	38 (33)	0.22
Past medical history			
Diabetes mellitus	313 (30)	35 (30)	0.98
Hypertension	658 (64)	68 (59)	0.34
Dyslipidaemia	606 (59)	58 (50)	0.090
Previous MI	264 (26)	36 (31)	0.18
Previous stroke	89 (8.6)	24 (21)	<0.001
Family history of CAD	104 (10)	0 (0)	<0.001
Smoker	517 (50)	48 (42)	0.091

Values are n (%) or median [interquartile range]. CAD indicates, coronary artery disease; MI, myocardial infarction.

Table S2. Reasons for Cardiac Catheterisation Laboratory Nonactivation

Variable	Frequency (n=464)
Nondiagnostic ST-segment elevation*	111 (24)
Artefact	66 (14)
RBBB without STEMI ECG criteria†	57 (12)
Preexisting LBBB	50 (11)
Repolarisation abnormality‡	47 (10)
Severe comorbid disease or advanced age	26 (5.6)
Absence of cardiac ischaemic symptoms	25 (5.4)
Transient ST-segment elevation	20 (4.3)
Inappropriate CCL nonactivation	19 (4.1)
Late presenting STEMI	13 (2.8)
Pericarditis	13 (2.8)
Received fibrinolytic therapy	10 (2.2)
Old MI	6 (1.3)
Patient refusal	1 (0.2)

Values are n (%). CCL indicates cardiac catheterisation laboratory; ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; STEMI, ST-segment elevation myocardial infarction.

* Nondiagnostic ST-segment elevation was defined as ≥0.5 mm and <1 mm in ≥1 lead.

† STEMI ECG criteria were defined as ST-segment elevation of ≥ 1mm (except ≥2 mm in men > 40 years, ≥2.5 mm in men <40 years or ≥1.5 mm in women in leads V2-3) in ≥2 contiguous leads.

‡ Repolarisation abnormalities included left ventricular hypertrophy, the early repolarisation pattern, Brugada pattern and paced rhythm.

Table S3. Diagnoses in Cardiac Catheterisation Laboratory Nonactivation Patients who had ST-segment Elevation Myocardial Infarction Electrocardiogram Criteria and Did Not Have an Adjudicated Index Diagnosis of ST-segment Elevation Myocardial Infarction

Variable	**Frequency** (n=57)
Transient (<20 min) ST-segment elevation	20 (35)
Pericarditis	14 (25)
Left ventricular hypertrophy	9 (16)
Old myocardial infarction	6 (11)
Early repolarisation pattern	4 (7.0)
Brugada pattern	2 (3.5)
Normal ST-segment elevation (male pattern)	1 (1.8)
Takotsubo cardiomyopathy	1 (1.8)

Values are n (%).

Table S4. Sensitivity Analysis: Clinical Outcomes at Two Years Stratified by Appropriate Cardiac Catheterisation Laboratory Nonactivation Versus Appropriate Cardiac Catheterisation Laboratory Activation

Variable	Appropriate CCL Activation (n=555)	Appropriate CCL Nonactivation (n=445)	Appropriate CCL Nonactivation Versus Activation	
			Unadjusted RR (95% CI)	Adjusted RR (95% CI)
All-cause death	42 (7.6)	107 (24)	3.18 (2.27-4.44)	1.65 (1.30-2.10)
Cardiovascular death/MI/stroke*	74 (13)	77 (17)	1.3 (0.97-1.74)	1.17 (0.90-1.50)
Cardiovascular death	34 (6.1)	57 (13)	2.09 (1.39-3.14)	1.36 (1.01-1.81)
MI	36 (6.5)	19 (4.3)	0.66 (0.38-1.13)	0.81 (0.49-1.26)
Stroke	11 (2.0)	12 (2.7)	1.36 (0.61-3.05)	1.20 (0.63-2.07)
Noncardiovascular death	8 (1.4)	50 (11)	7.79 (3.73-16.27)	1.70 (1.23-2.30)
Heart failure hospitalisation	11 (2.0)	47 (11)	5.33 (2.8-10.15)	1.51 (1.06-2.09)

Values are n (%) with RR (95% CI). Adjusted RR were obtained using a generalized linear model with a log link, Poisson error distribution, and adjusted for age, sex, diabetes mellitus, previous MI, previous stroke, cardiac arrest, bundle branch block, and troponin elevation. CI indicates confidence interval; MI, myocardial infarction, RR, risk ratio.

* A composite outcome of cardiovascular death/MI/stroke.

Table S5. Studies Examining the Diagnostic Accuracy of the University of Glasgow Algorithm for the Diagnosis of Myocardial Infarction

Author (year)	Population (n)	Reference Standard	Prevalence (%)	SN (%)	SP (%)	PPV (%)	NPV (%)
Willems (1991)[36]	Inhospital (929)	Echocardiography based criteria	59[†]	68	94	NR	NR
Macfarlane (2004)[37]	Emergency department (1220)	Conventional clinical criteria[*]	29[†]	47	99	NR	NR
Macfarlane (2007)[38]	Prehospital (1220)	Biomarker-based (BB) criteria and cardiologist assessment (CA)	BB: 20[†] CA: 9.3[‡]	BB: 54 CA: 89	BB: 98 CA: NA	NR	NR
Clark (2010)[§,39]	Prehospital (912)	Discharge diagnosis	STEMI: 34	78	93	87	89
Clark (2010)[§,40]	Prehospital (912)	Discharge diagnosis	STEMI: 34	78	94	87	89

Values are (year), (n) or %. BB indicates biomarker-based criteria for MI (includes STEMI and NSTEMI); CA, cardiologist assessment for presence of the 2007 ACC/ESC STEMI ECG criteria; SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; STEMI, ST-segment elevation myocardial infarction; NR, not reported and cannot be calculated from reported data.

* Not defined.

† Includes STEMI and NSTEMI.

‡ Based on cardiologist assessment for presence of the 2007 ACC/ESC STEMI ECG criteria without biomarker use. BB and CA were used as the reference standard for the diagnosis of MI in two separate analyses.

§ These were two separate studies that used the same test populations but tested different Glasgow algorithm STEMI ECG criteria.

Table S6. The Diagnostic Performance of the University of Glasgow Algorithm Compared to the Marquette-12SL Algorithm for the Diagnosis of Myocardial Infarction

Computer Algorithm	Sensitivity (%)	Specificity (%)
The University of Glasgow[36-40]	47 to 78	93 to 99
Marquette-12SL[36, 41-45]	52 to 78	91 to 100

Values are %.