Likelihood of myocardial infarction, revascularization and death following catheterization laboratory activation in patients with vs. without both chest pain and ST elevation

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Background Emergent cardiac catheterization laboratory activation (CCLA) for patients with suspected ST-elevation myocardial infarction (STEMI) is employed to expedite acute revascularization (AR). The incidence of false-positive CCLA, in which AR is not performed, remains high. The combination of chest pain (CP) and electrocardiographic ST elevation (STE) are the hallmarks of STEMI. However, CCLA is sometimes initiated for patients lacking this combination. The study objective was to quantify the difference in likelihood of AR and mortality in patients with vs. without both CP and STE.

Methods Retrospective analysis of 1621 consecutive patients for whom CCLA was initiated in a six-hospital network. We assessed the likelihood of acute myocardial infarction (AMI), presence of a culprit lesion (CL), performance of AR, and hospital mortality among patients with both CP and STE (+CP/+STE) compared with patients lacking one or both [non(CP/STE)].

Results 87.0% of patients presented with CP, 82.4% with STE, and 73.7% with both. Among +CP/+STE patients, AMI was confirmed in 90.4%, a CL in 88.9%, and AR performed in 83.1%. The corresponding values among non(CP/STE) patients were 35.8, 31.9, and 28.1%, respectively (P<0.0001 for each). Nevertheless, mortality among non(CP/STE) patients was three-fold higher than in +CP/+STE patients (13.3% vs. 4.5%; P < 0.0001), with non-coronary deaths 24-fold more likely.

Conclusion Patients lacking the combination of CP and STE have a markedly lower likelihood of AMI and AR than +CP/+STE patients, but significantly higher mortality. Protocols aimed at rapid, focused evaluation of non(CP/STE) patients prior to CCLA are needed. Coronary Artery Dis 2021, 32:197–204 Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.

Key words: cardiac catheterization, chest pain, myocardial infarction, percutaneous coronary intervention

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Introduction The benefit of acute revascularization (AR) by percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) is well-established [1,2]. Cardiac catheterization laboratory activation (CCLA) by an emergency department (ED) physician or paramedic prior to ED arrival has become routine for patients with ischemic symptoms and electrocardiographic ST-segment elevation (STE) [3]. However, false-positive (FP) CCLA, with no culprit lesion (CL) evident at angiography, continues to be reported in up to one-third of contemporary series [4–7]. Urgent catheterization of patients without a CL confers risk without corresponding likelihood of benefit. Such FP CCLA patients have a prognosis similar to, or worse than, those with occluded vessels [5,8–11]. Consequently, accurate identification and triage of patients with suspected STEMI remains an important goal. The presence of both chest pain (CP) and STE represents a simple and rapid triage tool for CCLA. Nevertheless, some patients present with non-CP symptoms, such as dyspnea or syncope, that could be consistent with acute myocardial ischemia. Similarly, presenting symptoms are sometimes sufficiently concerning to trigger CCLA despite the absence of STE. The impact of these deviations from a strict ‘CP and STE’ protocol on the likelihood of identifying a CL requiring AR is unknown. We identified the likelihood of acute myocardial infarction (AMI), the presence of a CL, and the performance of AR among patients with CP vs. non-CP presenting symptoms, and among those with

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vs. without STE, in whom CCLA was initiated in our hospital network. We also examined the occurrence and causes of in-hospital mortality in both groups.

Methods
This is a retrospective, observational, consecutive patient single network study. The study was approved by the network institutional review board, with a waiver of consent for the retrospective review of patient data. The St. Luke’s University Hospital Health Network MI Alert Registry has been maintained prospectively and includes all patients for whom CCLA was initiated since 2009. We reviewed clinical and angiographic data among all registry patients admitted to the six St. Luke’s University Network Hospitals from 1 January 2009 to 30 September 2016. Three of the hospitals have PCI-capable laboratories available on a 24-h basis 7 days per week basis. The remaining three hospitals transferred ED patients with possible STEMI to one of the PCI-capable facilities. CCLA was initiated by a single call to an operator who notified the laboratory staff. It was network policy to initiate CCLA for patients exhibiting CP and either STE or new left bundle branch block (LBBB) [3,12]; however, rigid adherence to predefined parameters was not mandated, and the invasive team was sometimes summoned under conditions outside strict protocol parameters. Data from the medical record of all registry patients were abstracted independently by two of the authors (data abstraction was shared equally by the first six authors). The paramedic record, ED physician and nursing notes, and admitting physician notes were carefully reviewed for the presence of CP. Shoulder, epigastric, and jaw pain were included in the +CP category. Other potentially ischemic symptoms, including dyspnea, palpitations, syncope, lightheadedness, fatigue, weakness, nausea, diaphoresis, or arrhythmia, in the absence of CP, constituted the non-CP category. The ECG that resulted in CCLA, including tracings obtained prior to ED arrival, was reviewed for the presence of at least 1 mm STE in two or more anatomically contiguous leads. LBBB constituted a separate ECG category. Angiographic results were categorized based on the report in the medical record. Other covariates included age, gender, ethnicity, chronic kidney disease [CKD, defined as estimated glomerular filtration rate (eGFR) <60 mL per minute per square meter], and prolonged cardiac arrest (defined as more than two episodes of cardiac defibrillation or more than 2 minutes of chest compressions). CCLA was defined as FP for AMI when AMI was not present in accordance with the Fourth Universal Definition of Myocardial Infarction [13]; FP for CL when no lesion >90%, or >50% showing definite angiographic evidence of thrombus, was present; and FP for AR if PCI was performed and surgical coronary artery bypass grafting (CABG) within 12 h of catheterization. Causes of death were as listed in the medical record.

To determine independent risk factors for the endpoints of AMI, identification of a CL, and performance of AR, we constructed three separate multivariate logistic regression models using SAS version 9.4 (Cary, North Carolina, USA). Since the unit of analysis was CCLA, we used generalized estimating equations with an independent correlation structure, given the small number of patients with multiple visits. We included the following categorical covariates: patient age (>65 vs. ≤65 years), sex, ethnicity (Caucasian vs. non-Caucasian), the presence of CP, ECG STE, LBBB, initial GFR (≥60 mL/min/M² vs. <60 mL/min/M²), and prolonged cardiac arrest. Prior to model construction, diagnostic assessment revealed possible confounding for initial eGFR in the AMI and CL models (based on >10% change in subsequent model parameter estimates); however, given its clinical importance, we retained initial eGFR as a covariate [14]. We reported adjusted odds ratios (AORs) and 95% confidence intervals with P < 0.05 denoting statistical significance, and no adjustment for multiple comparisons. We also conducted separate t-tests for proportions to compare groups with and without CP, STE, and LBBB for the co-primary outcomes of AMI, CL, and AR.

Results
There were 1684 CCLAs between 1 January 2009 and 30 September 2016. Sixty-three CCLAs occurred for hospital in-patients and were excluded from further analysis. Of the remaining 1621 patients, the mean age was 63.2 ± 13.8 (1 SD) years, and 1095 (67.6%) were male. AMI was confirmed in 1232 (76.0%); 1190 (73.4%) had a CL identified, and 1112 (68.6%) underwent AR. CP was present in 1410 (87.0%); 1335 (82.4%) had a CL without CP (AOR 9.05, 9.71, and 7.79 for AMI, CL, and AR, respectively; P < 0.0001 for each). Similarly, patients with CP were much more likely to have each of the three outcomes compared to patients without STE or LBBB (AOR 23.74, 20.42, and 14.58 for AMI, CL, and AR, respectively). Patients with STE were much more likely to have each of the three outcomes compared to patients without STE or LBBB (AOR 23.74, 20.42, and 14.58 for AMI, CL, and AR, respectively; P < 0.0001 for each). The likelihood of each of the three outcomes was far greater among patients with vs. those without CP (AOR 9.05, 9.71, and 7.79 for AMI, CL, and AR, respectively; P < 0.0001 for each). The likelihood of each of the three outcomes was far greater among patients with vs. those without CP (AOR 9.05, 9.71, and 7.79 for AMI, CL, and AR, respectively; P < 0.0001 for each). Similarly, patients with CP were much more likely to have each of the three outcomes compared to patients without STE or LBBB (AOR 23.74, 20.42, and 14.58 for AMI, CL, and AR, respectively; P < 0.0001 for each). The likelihood of each of the three outcomes was far greater among patients with vs. those without CP (AOR 9.05, 9.71, and 7.79 for AMI, CL, and AR, respectively; P < 0.0001 for each).
The registry included ‘all comers’ for whom CCLA was initiated. However, catheterization was not performed after system activation for 29 patients in the +CP/+STE group and 120 patients in the non(CP/STE) group. In most cases, cancelation was due to a perceived low likelihood of a CL by the cardiologist. In addition, 14 patients (3 with +CP/+STE) died before angiography could be performed, and another 11 (8 with +CP/+STE) were found to have a ‘no code’ status, refused catheterization, or had a terminal illness making aggressive therapy inappropriate. Because the option of revascularization had been removed in these patients, the outcomes were reanalyzed with patients who did not undergo catheterization.

The likelihood of AMI was markedly lower. Although there was an independent interaction of LBBB with all three outcomes (Table 1), the outcomes were lower (and in all cases ≤50%) for +CP/+LBBB than for +CP/+STE (Table 3), consequently, in subsequent analysis, patients with LBBB were grouped with the non(CP/STE) patients.

When the combination of CP and STE was compared with all other combinations of CP and ECG findings, the occurrence of these outcomes was markedly lower. Although there was an independent interaction of LBBB with all three outcomes (Table 1), the outcomes were lower (and in all cases ≤50%) for +CP/+LBBB than for +CP/+STE (Table 3), consequently, in subsequent analysis, patients with LBBB were grouped with the non(CP/STE) patients.

Because there was an interaction of ethnicity with outcome, the results were assessed separately among Caucasians vs. non-Caucasians, as well as among Hispanic patients, who made up 78.7% of the non-Caucasian population (Table 4). The likelihood of AMI was lower among non-Caucasians than Caucasians in both the +CP/+STE and non(CP/STE) groups (P = 0.004 for +CP/+STE). Regardless of ethnicity, there was a marked difference in the likelihood of AMI between the +CP/+STE and non(CP/STE) groups, with an absolute difference of 53.2% for Caucasians and 64.5% for non-Caucasians. There was a trend toward a lower likelihood of AR among non-Caucasians in the +CP/+STE group as compared with Caucasians, but the difference was NS (P = 0.17).

The registry included ‘all comers’ for whom CCLA was initiated. However, catheterization was not performed after system activation for 29 patients in the +CP/+STE group and 120 patients in the non(CP/STE) group. In most cases, cancelation was due to a perceived low likelihood of a CL by the cardiologist. In addition, 14 patients (3 with +CP/+STE) died before angiography could be performed, and another 11 (8 with +CP/+STE) were found to have a ‘no code’ status, refused catheterization, or had a terminal illness making aggressive therapy inappropriate. Because the option of revascularization had been removed in these patients, the outcomes were reanalyzed with patients who did not undergo catheterization.
the +CP/+STE group, 50 (92.6%) occurred due to AMI (Table 5). Among 57 deaths in non(CP/STE) patients, 26 (45.6%) were due to AMI, with 18 of 26 (69.2%) of AMI deaths occurring in patients who had sustained out of hospital (n = 14) or prolonged ED (n = 4) arrests. Deaths due to non-coronary causes were 22-fold more likely among non(CP/STE) than among +CP/+STE patients: 31 (7.3%) vs. 4 (0.3%), respectively. Deaths due to non-cardiovascular causes were 2-2 fold more likely among non(CP/STE) than among +CP/+STE patients: 19 (4.4%) vs. 2 (0.2%), respectively. Only eight non(CP/STE) patients (1.8%) presented without cardiac arrest and died due to coronary disease. The mean age of these eight patients was 84.5 years. Dementia was present in four; non-CP symptoms, including weakness or altered mental status, were present in five; one patient had CP, rapid atrial fibrillation and LBBB, one had CP and a non-diagnostic ECG with circumflex occlusion, and one had dyspnea, LBBB, and cardiogenic shock.

Because 31.9% of the non(CP/STE) group did have an identified CL and might potentially benefit from AR, we attempted to assess any characteristics that distinguish these patients from those in the non(CP/STE) group who did not have a CL. Among the non(CP/STE) patients who had CP without ST elevation, 29.6% had a culprit identified; 12.0% had a totally occluded culprit artery (Thrombolysis in Myocardial Infarction grade 0 or 1). There was no significant difference between those with a culprit vs. those without a culprit on angiography in the prevalence of known prior coronary disease (including prior MI, PCI, or CABG), which was present in 25% of

Table 4  Outcomes in +CP/+STE vs. non(CP/STE) patients by ethnicity

|                | +CP/+STE       |           | non(CP/STE) |           |
|----------------|----------------|-----------|-------------|-----------|
|                | N   | AMI (%) | CL (%) | AR (%) | N   | AMI (%) | CL (%) | AR (%) |
| Entire cohort  | 1194| 1079 (90.4) | 1054 (88.3) | 992 (83.1) | 427 | 153 (35.8) | 136 (31.9) | 120 (28.1) |
| Caucasian      | 995 | 910 (91.5) | 889 (89.3) | 833 (83.7) | 368 | 141 (38.3) | 126 (34.0) | 112 (30.4) |
| Non-Caucasian  | 197 | 167 (84.8)* | 163 (82.7) | 157 (79.7) | 59  | 12 (20.3)  | 11 (18.6)  | 8 (13.6)  |
| Hispanic       | 155 | 134 (86.5) | 131 (84.5) | 123 (79.4) | 34  | 5 (14.7)   | 5 (14.7)   | 4 (11.8)  |

+CP/+STE: patients presenting with both CP and STE; non(CP/STE): patients who did not present with both CP and STE.
AMI, acute myocardial infarction; AR, acute revascularization; CL, culprit lesion; CP, chest pain; STE, ST elevation.

*P = 0.004 vs. Caucasians.
those demonstrated to have a culprit vs. 32% of those without a culprit. However, the group without a CL was significantly more likely to have dyspnea on presentation than the group in whom a culprit was present (69% vs. 48%; \( P < 0.01 \)). Because circumflex occlusions are sometimes ‘electrically silent’, failing to produce STE on the ECG, we assessed the frequency of circumflex occlusion in this subpopulation. The proportion of totally occluded circumflex culprit arteries was not significantly different among the patients with CP but without STE who were found to have a culprit (12.5%) than among the patients with both CP and STE who had a culprit (8.4%; \( P = 0.26 \)). Although the group with CP but without STE was dominated by patients without a clear culprit, they were not uniformly free of coronary disease. 11.5% of patients in this group had multivessel disease with no clear culprit artery and underwent non-urgent surgical revascularization a mean of 4.2 ± 1.8 days after catheterization.

Non-ischemic diagnoses other than non-cardiac CP among patients in this group who did not have a culprit were congestive heart failure due to cardiomyopathy (7%); 5% non-ischemic), stress cardiomyopathy (6%), LVH (4%), aortic dissection (2%), and drug-seeking behavior (2%).

Among the non(CP/STE) patients undergoing catheterization who had STE without CP, a culprit was present in 62%; a totally occluded culprit was present in 34%. Compared to those who did not have a culprit evident on angiography, patients having a culprit more often presented after having sustained a ventricular fibrillation (VF) arrest (36.9% vs. 17.5%; \( P = 0.03 \)). Of the patients without a culprit who presented with VF, three had normal coronary arteries and four had known cardiomyopathies without a new CL. There was no significant difference
between those with a culprit and those without a culprit in the frequency of dyspnea as a presenting symptom (24.6% vs. 20.0%, respectively) or in other non-CP symptoms, including nausea/vomiting, diaphoresis, or lightheadedness/syncope. A distinct subset among -CP/+STE patients found to have a culprit were elderly patients who presented with weakness, altered mental status, or confusion without CP; all were octogenarians or nonagenarians; this accounted for 10.7% of the -CP/+STE patients with a CL. This clinical presentation appeared to be highly specific; all patients in this group were found to have a culprit. Among non(CP/STE) patients who had STE without a culprit, 75% had normal coronaries or minimal plaque, including 17.5% with stress cardiomyopathy, 7.5% with early repolarization syndrome, and 5% with pulmonary embolus. A chronic total occlusion was present in 12.5% of patients with no clear culprit, and was felt to be responsible for transient or chronic ST elevation in most of these patients. Ten percent of patients with no definite culprit had multivessel disease without evidence of acute thrombosis or occlusion and underwent or bypass surgery from 3 to 7 days after admission.

Discussion

The association of acute thrombotic occlusion of an epicardial vessel as the pathogenic event in STEMI was demonstrated by DeWood et al. [15]. The benefit of early reperfusion by thrombolysis [16] or PCI [17] was subsequently established. CCLA by an ED physician or paramedic is a widely employed strategy for shortening the time to reperfusion. However, this approach is associated with FP rates ranging from 10 to 36% [4,5,8,18–20].

Some of the heterogeneity in reported rates of FP CCLA reflects varying criteria for study inclusion or the definition of ‘false-positive’. Several reports excluded patients who were retrospectively identified as not having STE [11,21], or distinguished between ‘inappropriate’ and ‘appropriate’ false activations [4,6,9,20,22]. We selected a strict definition of FP CCLA, since, in the absence of a culprit artery, urgent catheterization is likely to carry limited benefit and potential harm.

Misinterpretation of ECG findings is a common cause of FP CCLA [12,21]. Some FP CCLAs may be unavoidable, including patients having takotsubo cardiomyopathy, pericarditis, or early repolarization syndrome [8,10,23,24]. In the study of Larson et al. [18], in which only 1.8% of patients did not have STE, 85.3% had a definite CL, suggesting that more rigid adherence to an STE criteria can yield a low FP rate.

While the ECG has been well-studied as a criterion for CCLA, relatively little attention has been directed to CP. Other associated symptoms are sometimes encountered in patients suffering AMI, including dyspnea, nausea, vomiting, diaphoresis, lightheadedness, or syncope [25,26]. In patients without CP, these are sometimes regarded as ‘anginal equivalents’. Nfor et al. [8] demonstrated an AOR of 18.2 for the absence of a CL among patients having STE without CP. Kim et al. [21] reported an AOR of 12.0 for FP CCLA among nonCP patients; 17.6% of patients in that cohort presented without CP, similar to the 13.0% in our cohort. In the Activate-SF Registry, CP was associated with an AOR of 0.28 for FP CCLA [5]. Among 484 877 patients in the National Registry of Myocardial Infarction 2, MI presentation without CP was twice as common among patients with NSTEMI as among patients with STEMI, suggesting that the absence of CP may reflect vessel patency [27]. Although patients with STEMI benefit from AR, emergent catheterization is not necessary for patients with non-STE ACS [28]. Consequently, the 28.1% rate of AR in our non(CP/STE) patients probably represents an overestimate of the need for AR in this group.

In our cohort, Caucasian ethnicity was associated with higher rates of AMI, CL, and AR, both in the +CP/+STE and the non(CP/STE) groups. The reason for the difference is uncertain. A higher incidence of FP CCLA among non-whites has been reported by others [4,5,28]. Because Hispanics constituted more than three-quarters of the non-Caucasian population in our cohort, it is possible that some of the difference was the result of a language barrier. Although a telephonic translation service is available in our facilities, its use can be cumbersome, and its application in the setting of STEMI, with the attendant time pressure, is not routine. Often, bilingual family members or hospital staff provided translation.

The patients presenting without both CP and STE constituted a heterogeneous group. The significantly higher prevalence of dyspnea among the non(CP/STE) patients who had CP without STE and had no culprit artery identified at angiography suggests that this non-CP symptom, which could be the result of numerous potential mechanisms, might trigger CCLA for a patient at low risk of having an occluded vessel. 88% of non(CP/STE) patients who presented with CP but without STE had either no culprit or an NSTEMI with an incomplete occlusion. Among the patients who presented with STE but not CP, presentation with cardiac arrest suggested the presence of a CL, and early angiography is recommended in such cases. Very elderly patients presenting with altered mental status or confusion uniformly had CLs. Outside of these clinical circumstances, a substantial variety of diagnoses were encountered, including stress cardiomyopathy, early repolarization syndrome, and pulmonary embolus.

There are numerous drawbacks to FP CCLA. Unnecessary catheterization is wasteful of limited resources. However, the most serious concern is the potential for harm to patients having a serious acute illness other than AMI that is not identified because of an initial approach that is too narrowly focused. In addition
to the risks inherent in invasive angiography, CCLA in a patient seriously ill with a non-coronary illness may delay appropriately directed diagnostic modalities. Patients for whom CCLA is initiated may receive only an abbreviated review of their history and presenting symptoms in the catheterization laboratory. The physical examination may be cursory in a patient covered with sterile drapes when first encountered. Mortality rates as high as 16% [26] and 21.6% [11] have been reported among patients with FP CCLA, similar to our findings. Diagnoses in these patients included aortic dissection and subarachnoid hemorrhage [26], which could be complicated by the anticoagulation employed in the course of CCLA. CKD may be exacerbated by contrast administration without preparatory hydration. In our study, the in-hospital mortality was nearly three-fold higher in the non(CP/STE) patients than those who were +CP/+STE. Among +CP/+STE patients, 92.6% of deaths were due to AMI; non-coronary deaths occurred in four patients (0.3%), as compared with 31 (7.3%) of those without both CP and STE. Non-cardiovascular deaths occurred in 0.2% of +CP/+STE patients vs. 4.9% of the non(CP/STE) group.

Patients presenting after cardiac arrest constitute a special subgroup of CCLAs. A history of CP is often not available in these patients. Current guidelines recommend urgent catheterization if STE is present [29]. A recent study indicated that patients presenting with cardiac arrest without STE do not benefit from revascularization [30]. In our registry, 20 patients in the non(CP/STE) group who presented without cardiac arrest subsequently died, the majority of a non-coronary etiology. Among the eight deaths due to coronary disease, all but one were very elderly, most presenting with nonCP symptoms including weakness or altered mental status.

To our knowledge, this is the first study to quantify the substantial degradation in the likelihood of identifying a CL and performing AR associated with deviation from a CCLA protocol limited to patients having both CP and STE. These outcome differences, and the high non-coronary mortality among non(CP/STE) patients, suggests the need for modified CCLA protocols. One algorithm might be a staged, or tiered, triage protocol, in which CCLA is initiated in +CP/+STE patients, with an urgent focused consultation for patients not meeting these criteria. Such a consultation would include a quick assessment for alternative etiologies in patients for whom the diagnosis of STEMI appears equivocal. Although this might incur a short delay, there is evidence that modest differences in door to balloon times have limited effect on outcome [31–33].

Our study has several limitations. It was observational, and therefore useful for hypothesis-generation. Confirmation of these findings at other institutions, including a broader geographic distribution, is warranted. A randomized trial of alternative protocols, including the tiered approach described above, would appear to be appropriate. The patients included were those in whom CCLA was initiated; patients in whom the diagnosis of STEMI was missed and were admitted to the hospital with another diagnosis, including non-STE ACS, or who were not admitted to the hospital, would not be included in this registry. Chest discomfort is a subjective phenomenon; its inclusion depended on the reliability of the patient in reporting symptoms and the thoroughness of the individuals documenting the history. Our data, as well as that of other investigators, probably overestimates the need for AR in patients who do not have STE, since patients with NSTEMI, who do not require emergent PCI but typically have flow-significant stenoses, will commonly undergo revascularization if CCLA occurs. The extent to which the higher mortality in the non(CP/STE) group was related to an initial diagnostic approach that was focused on a coronary etiology rather than the actual non-coronary cause of death cannot be determined from our data. Our non-Caucasian population was predominantly Hispanic; representation of African-American patients and patients of other ethnicities was too low to permit meaningful conclusions.

We conclude that presence of both CP and STE represents a simple, rapid, and accurate screening tool for the identification of ED patients having a high likelihood of AMI and need for AR. Patients presenting with symptoms other than CP, or an ECG that does not exhibit at least 1 mm STE in two anatomically contiguous leads, have a markedly lower likelihood of having AMI and requiring AR. Such patients constitute a heterogeneous group with a high risk of in-hospital mortality, with most deaths being non-cardiac in etiology. The need for routine CCLA in such patients is not established, may increase risk, and delay appropriately directed diagnostic modalities. Alternative protocols may be warranted in such patients.

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