Original Article

Impact of STEMI Diagnosis and Catheterization Laboratory Activation Systems on Sex- and Age-Based Differences in Treatment Delay

Christine Pacheco, MD, MSc,[a,b] Laurie-Anne Boivin-Proulx, MD,[b,c] Alexandra Bastiany, MD,[d]

Alexis Matteau, MD, SM,[b,c] Samer Mansour, MD,[b,c] François Gobeil, MD,[b]

Oana-Maria Simion, MD,[e] André Kokis, MD,[b] C. Noel Bairey Merz, MD,[f] and

Brian J. Potter, MDCM, SM[b,c]

[a] *Hôpital Pierre-Boucher, Université de Montréal, Montréal, Québec, Canada*

[b] *Centre Hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada*

[c] *Centre de Recherche du CHUM (CRCHUM), Montréal, Québec, Canada*

[d] *Thunder Bay Regional Health Sciences Centre, Thunder Bay, Ontario, Canada*

[e] *Hôpital Maisonneuve-Rosemont, Montréal, Québec, Canada*

[f] *Barbra Streisand Women's Heart Center, Cedars-Sinai Smidt Heart Institute, Los Angeles, California, USA*

ABSTRACT

Background: Women and the elderly with ST-elevation myocardial infarction (STEMI) experience longer treatment delays despite prehospital STEMI diagnosis and catheterization laboratory activation systems. It is not known what role specific STEMI referral systems might play in mediating this gap in care. We therefore examined sex- and age-based differences in STEMI treatment delay (TD) in different STEMI activation systems.
Methods: This observational comparative effectiveness study comprised 3 retrospective STEMI cohorts: a traditional hospital-based

RÉSUMÉ

Introduction : Les femmes et les personnes présentant ont un infarctus du myocarde avec élévation du segment ST (STEMI) subissent de plus longs retards de traitement en dépit du diagnostic préhospitalier de STEMI et des systèmes d'activation de laboratoires de cathétérisme. On ignore le rôle que pourraient jouer les systèmes d'aiguillage des personnes atteintes de STEMI pour combler cette lacune en matière de soins. Nous avons donc examiné les différences selon le sexe et l'âge dans le retard de traitement du STEMI des différents systèmes d'activation de laboratoire en présence de STEMI.

Despite significant advances in treatment, both women and older patients diagnosed with ST-elevation myocardial infarction (STEMI) continue to experience suboptimal

treatment delays (TD)[1-3] and higher rates of adverse outcomes.[3-5] This persistent gap is often attributed to atypical symptoms,[6,7] longer delays between symptom onset and diagnosis,[3,8,9] and less frequent use of invasive testing than in younger patients[5] and men.[10] Longer door-to-device times and first medical contact-to-device times (FMC-to-device) are associated with increased mortality following STEMI,[2,11] and these delays have been reported to be significantly longer for women and older patients.[5,12,13] Prehospital electrocardiographic STEMI diagnosis[14,15] and prehospital cardiac catheterization laboratory (CCL) activation[16] have led to a significant reduction in overall TD. However, although some reports suggest that STEMI diagnosis and CCL activation standardization may reduce the TD gap and differences in outcomes between women and men,[17,18] other studies continue to show longer FMC-to-device times for women with prehospital activation systems,[2] with little information

activation cohort (Cohort 1), an automated "physician-blind" pre-hospital activation cohort (Cohort 2), and a prehospital activation with real-time physician oversight cohort (Cohort 3). Outcomes of interest included sex and age group ($<$ or $\geq$ 75 years) differences in subopti-mal ($>$ 90 minutes) first medical contact-to-device time (FMC-to-de-vice) within each cohort, as well as independent predictors of suboptimal FMC-to-device and in-hospital mortality across cohorts.

Results: Five hundred-sixty STEMI activations were analyzed. In Cohort 1 (n = 179), women and those $\geq$ 75 were more likely to experience suboptimal FMC-to-device times (78.7% vs 36.4%, P = 0.02 and 85.0% vs 58.3%, $<$ 0.01, respectively). Similar findings were observed in Cohort 3 (n = 109) (53.5% vs 32.9%, 56.5% vs 33.3%, respectively; P = 0.05, for both). In Cohort 2 (n = 272), however, there was no significant age-based difference (30.4% vs 21.7%, P = 0.18), and the gap was numerically lower but still significant for women (32.1% vs 20.1%, P = 0.04). When examining prehospital activation cohorts only, female sex (P = 0.03), off-hours presentation ($P <$ 0.01), and physi-cian oversight ($P <$ 0.01) were independent predictors of longer FMC-to-device times. Age $\geq$ 75 ($P <$ 0.01), Killip class ($P <$ 0.01), and female sex (P = 0.04) were independently associated with in-hospital mortality.

Conclusions: Automated "physician-blind" STEMI activation was associated with a reduced TD gap in women and the elderly, sug-gesting possible systemic bias. Appropriately powered confirmatory studies are required, but incorporating automated diagnosis and catheterization laboratory activation may be a solution to treatment gaps in STEMI care.

Méthodes : La présente étude comparative sur l'efficacité regroupait trois cohortes rétrospectives de STEMI : une cohorte traditionnelle d'activation à l'hôpital (cohorte 1), une cohorte d'activation du labo-ratoire lors de diagnostic préhospitalier automatisé « à l'insu du médecin » (cohorte 2) et une cohorte d'activation du laboratoire de diagnostic préhospitalier dont la surveillance est assurée par un médecin en temps réel (cohorte 3). Les critères d'intérêt étaient les différences selon le sexe et le groupe d'âge ($<$ ou $\geq$ 75 ans) dans le taux d'intervalle sous-optimal entre la première prise de contact avec les services médicaux et la pose d'un dispositif ($>$ 90 minutes) au sein de chaque cohorte, ainsi que les prédicteurs indépendants de l'intervalle sous-optimal entre la première prise de contact avec les services médicaux et la pose d'un dispositif et la mortalité à l'hôpital de toutes les cohortes.

Résultats : Cinq cents soixante (560) activations de diagnostic de STEMI ont fait l'objet d'une analyse. Dans la cohorte 1 (n = 179), les femmes et les personnes $\geq$ 75 ans étaient plus susceptibles de subir des intervalles sous-optimaux entre la première prise de contact avec les services médicaux et la pose d'un dispositif (78,7 % vs 36,4 %, P = 0,02 et 85,0 % vs 58,3 %, $<$ 0,01, respectivement). Nous avons observé des résultats similaires dans la cohorte 3 (n = 109) (53,5 % vs 32,9 %, 56,5 % vs 33,3 %, respectivement ; P = 0,05, pour les deux). Toutefois, dans la cohorte 2 (n = 272), il n'y avait aucune différence significative selon l'âge (30,4 % vs 21,7 %, P = 0,18) et l'écart était numériquement plus faible, mais encore significatif chez les femmes (32,1 % vs 20,1 %, P = 0,04). Lorsque nous examinions seulement les cohortes d'activation du laboratoire lors de diagnostic préhospitalier, le sexe féminin (P = 0,03), la survenue dans les heures creuses ($P <$ 0,01) et la surveillance du médecin ($P <$ 0,01) étaient des prédicteurs indépendants d'intervalles plus longs entre la première prise de con-tact avec les services médicaux et la pose d'un dispositif. L'âge $\geq$ 75 ans ($P <$ 0,01), la classification de Killip ($P <$ 0,01) et le sexe féminin ($P <$ 0,04) étaient indépendamment associés à la mortalité à l'hôpital.

Conclusions : L'activation du laboratoire lors de diagnostic automatisé du STEMI « à l'insu du médecin » a été associée à une réduction de l'écart dans le retard de traitement chez les femmes et les personnes âgées. Ceci indique un possible biais systémique. Des études con-firmatives d'une puissance suffisante sont nécessaires, mais l'incor-poration du diagnostic et de l'activation du laboratoire de cathétérisme atuomatisés peut être une solution aux écarts de traitement dans les soins de STEMI.

on the impact of such systems in older patients. In some Canadian hospital networks, automated prehospital STEMI diagnosis and CCL activation systems without real-time physician oversight have been implemented and are highly effective in ensuring the achievement of target TD in the majority of patients.[19,20] We explored sex- and age-based differences in achieving optimal TD in different STEMI-activation systems and whether a "physician-blind" system might be associated with reduced TD gaps for women and the elderly.

Methods

We conducted a retrospective, dual-centre all-comers observational study of patients with confirmed STEMI. Both centres are community hospitals in the Greater Montréal Area with a stand-alone (no on-site surgical backup) CCL. The first centre (A) served a geographic region of 246 km^2 (population of approximately 440,000).[21] The second centre (B) served an

area of 11 112 km (population of approximately 1,551,000).[22] In both systems, any patient with a chief complaint of chest pain or dyspnea had an in-the-field elec-trocardiogram (ECG) performed by an ambulance technician. (Ambulance technicians are trained in the proper acquisition of an ECG, but not in ECG interpretation in the province of Québec.) In Centre A, an automated diagnosis of acute myocardial infarction (ZOLL E Series monitor-defibrillator; Zoll Medical Corporation, Chelmsford, MA) led to auto-matic CCL team activation (simultaneous paging system) by the ambulance technician and direct patient transfer to the CCL without transmission or reinterpretation of the ECG by a physician before patient arrival. Patients with tachycardia $>$140 beats per minute (bpm), left bundle branch block, and paced rhythm were excluded from the automated activation protocol to minimize the risk of inappropriate activation.[19,20] In Centre B, the prehospital activation system was identical, except that the prehospital ECG was

Pacheco et al.
STEMI Activation Systems and Treatment Gaps

725

transmitted to the receiving centre active on-duty emergency physician for interpretation and who ultimately decided whether to activate the CCL. For reasons of patient confidentiality, the emergency physician did not have access to identifying information or medical records before arrival at the hospital but was apprised of the clinical presentation. Interventional cardiologists did not review the ECG before arriving at the hospital with the CCL team. The interventional cardiologist could choose not to proceed with coronary angiography upon evaluation of the patient and ECG, but only after the patient had arrived at the percutaneous coronary intervention (PCI) centre and the CCL team had been mobilized.

Two cohorts were created at Centre A. Cohort 1 was a traditional hospital-based activation cohort, established before the implementation of a prehospital diagnosis of STEMI and CCL activation protocol described here. Consecutive patients presenting with confirmed STEMI were enrolled in this cohort from May 2007, to January 2009. Also from Centre A, Cohort 2 consisted of patients presenting following the implementation of a second iteration of an automated physician-blind prehospital STEMI diagnosis and CCL activation protocol (January 2012, to December 2013).[19,20] Cohort 3 was established at Centre B and comprised patients identified in the prehospital setting but with real-time physician oversight of CCL activation through ECG transmission as described ("physician-aware," July 2014, to August 2015). For all 3 cohorts, data were collected by a combination of prospective CCL STEMI registries and chart review. Baseline characteristics included age at diagnosis, sex, cardiovascular risk factors, history of coronary artery disease (CAD) or previous coronary artery bypass graft (CABG), and chest pain as presenting symptoms. Patients were considered elderly if they were aged 75 years or older. Confirmed STEMI was defined per current guidelines as ST-elevation in 2 contiguous leads ($\geq$ 2 mm for men and $\geq$ 1.5 mm for women in in leads V2-V3 and $\geq$ 1 mm in other leads),[23] associated with a significant coronary lesion or altered thrombolysis-in-myocardial-infarction flow in a corresponding coronary artery. All ECGs were independently reviewed by 2 researchers (among C.P., A.B., L.A.B.P.) blinded to the results of angiography. None of the primary ECG evaluators was involved in STEMI care at either centre. Any instance of discordant interpretation was reviewed by a third researcher (B.J.P.). Time of first medical contact was defined as the time of first contact as noted in the ambulance technician records. Door time was defined as the time of arrival noted in emergency triage records. Device time was defined as the time of first activation of an intracoronary device (balloon inflation, stent deployment, or thrombus aspiration) according to the CCL procedure log (timepieces were not synchronized). FMC-to-device time was calculated by subtracting first medical contact time from device time, and door-to-device time was calculated by subtracting door time from device time. Data on all-cause in-hospital mortality and medications at discharge were also collected.

The primary outcome of interest was sex and age-based differences in FMC-to-device categories ($\leq$ 90 minutes [optimal] vs > 90 minutes [suboptimal]; ie, women vs men and elderly $\geq$ 75 years vs nonelderly < 75 years). Other outcomes of interest included door-to-device times using the same 90-minute cutoff ($\leq$ 90 minutes [optimal] vs > 90 minutes [suboptimal]), as these were the recommended door-to-device delays in society guidelines at the time of data collection.[23] We also sought to determine independent predictors of suboptimal TD both with and without physician involvement and independent predictors of in-hospital mortality.

Statistical analyses

Continuous variables and categorical variables are presented as means (standard deviation [SD]) or medians (interquartile range [IQR]) and compared using Student's t-tests, Wilcoxon rank-sum tests, or χ^2 tests, as appropriate. Multivariate analysis of predictors of suboptimal TD was conducted across both prehospital activation cohorts (Cohorts 2 and 3 only, as including Cohort 1, which consisted solely of hospital-based activations in this analysis, would have biased against physician oversight. Covariates were included based on a combination of expert opinion and results of univariate analyses (P < 0.05). Multivariate predictors of in-hospital mortality across both prehospital cohorts were also examined using logistic regression models. In exploratory analyses, multivariate predictors of suboptimal TD and mortality across all 3 cohorts were examined (Supplemental Table S1), as well as predictors of both suboptimal TD and mortality in cohorts with physician involvement only (Cohorts 1 and 3) (Supplemental Tables S2 and S3). TD variables (FMC-to-device and door-to-device) were specifically not included as covariates in the primary mortality model, as differential TD was posited to be on the causal pathway between both female sex and older age and in-hospital mortality. The variance inflation factor was used to examine for collinearity between demographic variables (age and sex).[24] To examine for a possible interaction between age group and sex, multivariate logistic regression models excluding either sex or age were compared with the model, including both variables or an interaction term using a likelihood ratio test. Statistical analysis was performed using STATA software (version 14.2; STATA Corp, College Station, TX).

Results

In the traditional hospital-based STEMI activation cohort (Cohort 1, Centre A), 189 patients with confirmed STEMI were identified, of whom 10 did not have PCI (all had spontaneous reperfusion and were referred for CABG), resulting in 179 cases with FMC-to-device and door-to-device times. In the automated prehospital STEMI activation cohort (Cohort 2, Centre A), 277 patients with confirmed STEMI were identified, of whom 5 did not have PCI (1 case treated medically because of significant comorbidity; 4 cases referred for CABG), resulting in 272 cases with FMC-to-device and door-to-device times. In the prehospital STEMI activation with physician oversight cohort (Cohort 3, Centre B), 113 patients with confirmed STEMI were identified, of whom 4 did not undergo any intervention (spontaneous coronary artery dissection [n = 1], inability to perform PCI [n = 1]; referred for CABG [n = 2]), resulting in 109 cases with FMC-to-device and door-to-device times.

Baseline patient characteristics in each cohort according to patient sex and age group are presented in Tables 1 and 2.

Table 1. Baseline patient characteristics according to sex, across 3 independent cohorts

	Cohort 1 Hospital-based activation with physician oversight (Centre A) 2007-2009 (N = 179)			Cohort 2 Automated prehospital activation (Centre A) 2012-2014 (N = 272)			Cohort 3 Prehospital activation with physician oversight (Centre B) 2014-2015 (N = 109)		
	Women (N = 47)	Men (N = 132)	P value	Women (N = 78)	Men (N = 194)	P value	Women (N = 30)	Men (N = 79)	P value
Age (years)	71.2 (± 14.4)	58.9 (± 11.6)	< 0.01*	70.2 (± 12.7)	60.0 (± 11.5)	< 0.01*	71.0 (± 12.5)	61.4 (± 11.2)	< 0.01*
Smoking	12 (25.5%)	58 (43.9%)	0.03*	35 (44.9%)	94 (48.5%)	0.59	10 (33.3%)	32 (40.5%)	0.49
Hypertension	29 (61.7%)	59 (44.7%)	0.05*	53 (68.0%)	92 (47.4%)	< 0.01*	19 (63.3%)	23 (29.5%)	< 0.01*
Diabetes	9 (19.2%)	33 (25.0%)	0.42	18 (23.1%)	26 (13.4%)	0.05	10 (33.3%)	11 (13.9%)	0.02*
Dyslipidemia	19 (40.4%)	69 (52.3%)	0.16	35 (44.9%)	118 (60.8%)	0.02*	14 (46.7%)	29 (36.7%)	0.34
"Off-hours" presentation[†]	33 (70.2%)	86 (65.2%)	0.53	54 (69.2%)	125 (64.8%)	0.48	17 (56.7%)	44 (55.7%)	0.93
Anterior MI	25 (53.2%)	51 (38.6%)	0.08	21 (27.3%)	50 (26.0%)	0.84	4 (13.3%)	26 (32.9%)	0.04*
Killip III-IV	7 (14.9%)	17 (12.8%)	0.73	12 (15.4%)	13 (6.7%)	0.03*	2 (7.1%)	7 (9.0%)	0.77
Chest pain	42 (89.4%)	126 (95.5%)	0.14	73 (93.6%)	190 (98.4%)	0.03*	28 (96.5%)	79 (100.0%)	0.10

Data are presented as mean (± standard deviation) or counts (n) and the percent proportion. Centre A - CCL cohort, missing values: chest pain: men = 1; off-hours presentation: men = 1. Centre B - CCL physician oversight cohort, missing values: chest pain: women = 1; Killip: women = 2, men = 1; hypertension: men = 1.

FMC-to-device, first medical contact-to-device time; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

* $P < 0.05$.

[†] "Off-hours" was defined as any case occurring outside of normal working hours (8AM to 4PM) for that centre, as well as weekends and holidays.

Median TD according to sex and age are presented in Figure 1 and Figure 2, respectively. In the traditional hospital-based activation cohort (Cohort 1, Centre A), women experienced a higher proportion of suboptimal TD than men (Table 3). When analyzed continuously, median (IQR) TD was longer in women (door-to-device: 94.5 (66.5) minutes vs 83.6 (42.5) minutes in men, $P = 0.01$; FMC-to-device: 119.9 (49.6) minutes vs 103.0 (44.9) $P < 0.01$). Those aged ≥ 75 also experienced a higher proportion of suboptimal TD (Table 3), and median TD was longer (door-to-device: 99.2 [29.9] minutes vs 79.8 [45.1], $P < 0.01$, FMC-to-device: 125.8 [45.1] minutes vs 101.0 [43.0], $P < 0.01$).

In Cohort 2 (Centre A), in which prehospital CCL activation was automated and occurred without real-time physician oversight, similar proportions of women and men had suboptimal door-to-device times (Table 3). Although women also experienced a higher proportion of suboptimal

FMC-to-device times in Cohort 2 ($P = 0.04$), the care gap was smaller than in other cohorts. When analyzed continuously, TD remained longer in women, but median TD was below 90 minutes (door-to-device: 50 [21] min vs 43 [24], $P < 0.01$; FMC-to-device: 80.5 [31] minutes vs 74 [26] minutes, $P = 0.02$). There was no difference according to age group in this cohort (Table 3). Median door-to-device, but not FMC-to-device, was longer in those ≥ 75 years of age, but below 90 minutes (door-to-device: 50 [25.5] minutes vs 44.5 [23] minutes, $P = 0.04$; FMC-to-device: 79 [31.5] minutes vs 75 [24.5] minutes, $P = 0.13$).

In Cohort 3 (Centre B), comprising prehospital activations with real-time physician oversight, women also experienced a higher proportion of suboptimal TD than men (Table 3). Median FMC-to-device remained longer than 90 minutes in women in this cohort, with a trend for statistical significance (door-to-device: 60 [31] minutes vs 50 [20] minutes,

Table 2. Baseline patient characteristics according to age, across 3 independent cohorts
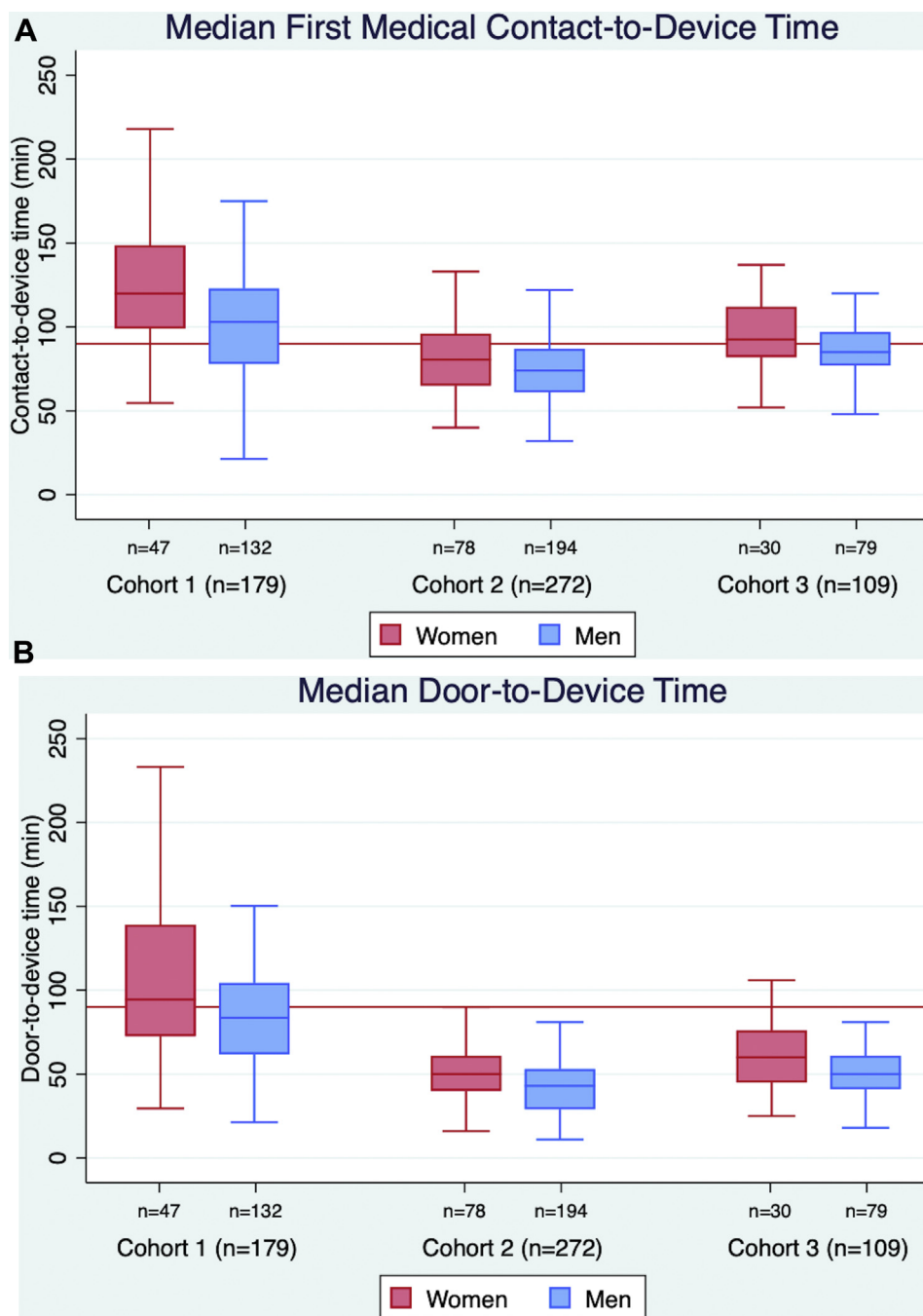
	Cohort 1 Hospital-based activation with physician oversight (Centre A) 2007-2009 (N = 179)			Cohort 2 Automated prehospital activation (Centre A) 2012-2014 (N = 272)			Cohort 3 Prehospital activation with physician oversight (Centre B) 2014-2015 (N = 109)		
	< 75 years N = 139	≥ 75 years N = 40	P value	< 75 years N = 216	≥ 75 years N = 56	P value	< 75 years N = 86	≥ 75 years N = 23	P value
Women	25 (18.0%)	22 (55.0%)	< 0.01*	46 (21.3%)	32 (57.1%)	< 0.01*	18 (20.9%)	12 (52.2%)	< 0.01*
Smoking	67 (48.2%)	3 (7.5%)	< 0.01*	112 (51.9%)	17 (30.4%)	< 0.01*	41 (47.7%)	1 (4.4%)	< 0.01*
Hypertension	62 (44.6%)	26 (65.0%)	0.02*	102 (47.2%)	43 (76.8%)	0.02*	29 (33.7%)	13 (59.1%)	0.03*
Diabetes	33 (23.7%)	9 (22.5%)	0.87	29 (13.4%)	15 (26.8%)	0.04*	17 (19.8%)	4 (17.4%)	0.80
Dyslipidemia	70 (50.4%)	18 (45.0%)	0.55	128 (59.3%)	25 (44.6%)	0.05	30 (34.9%)	13 (56.5%)	0.06
"Off-hours" presentation[†]	91 (65.5%)	28 (70.0%)	0.59	144 (67.0%)	35 (62.5%)	0.85	45 (52.3%)	16 (69.6%)	0.14
Anterior MI	53 (38.1%)	23 (57.5%)	0.03*	56 (26.2%)	15 (27.3%)	0.87	23 (26.7%)	7 (30.4%)	0.73
Killip III-IV	18 (13.0%)	6 (15.0%)	0.74	16 (7.4%)	9 (16.1%)	0.05	7 (8.3%)	2 (9.1%)	0.91
Chest pain	129 (92.8%)	39 (97.5%)	0.28	211 (98.1%)	52 (92.9%)	0.04*	85 (100.0%)	22 (95.7%)	0.05

Data are presented as counts (n) and the percent proportion. Centre A - CCL cohort, missing values: chest pain < 75 = 1; "off-hours" presentation < 75 = 1; anterior MI < 75 = 1, ≥ 75 = 2. Centre B - CCL physician oversight cohort, missing values: hypertension ≥75 = 1; Killip < 75 = 2, ≥ 75 = 1; chest pain < 75 = 1.

FMC-to-device, first medical contact-to-device time; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

* $P < 0.05$.

[†] "Off-hours" was defined as any case occurring outside of normal working hours (8 AM to 4 PM) for that centre, as well as weekends and holidays.

Pacheco et al.
STEMI Activation Systems and Treatment Gaps

727

A

Median First Medical Contact-to-Device Time

n=47   n=132   n=78   n=194   n=30   n=79
Cohort 1 (n=179)   Cohort 2 (n=272)   Cohort 3 (n=109)

■ Women ■ Men

B

Median Door-to-Device Time

n=47   n=132   n=78   n=194   n=30   n=79
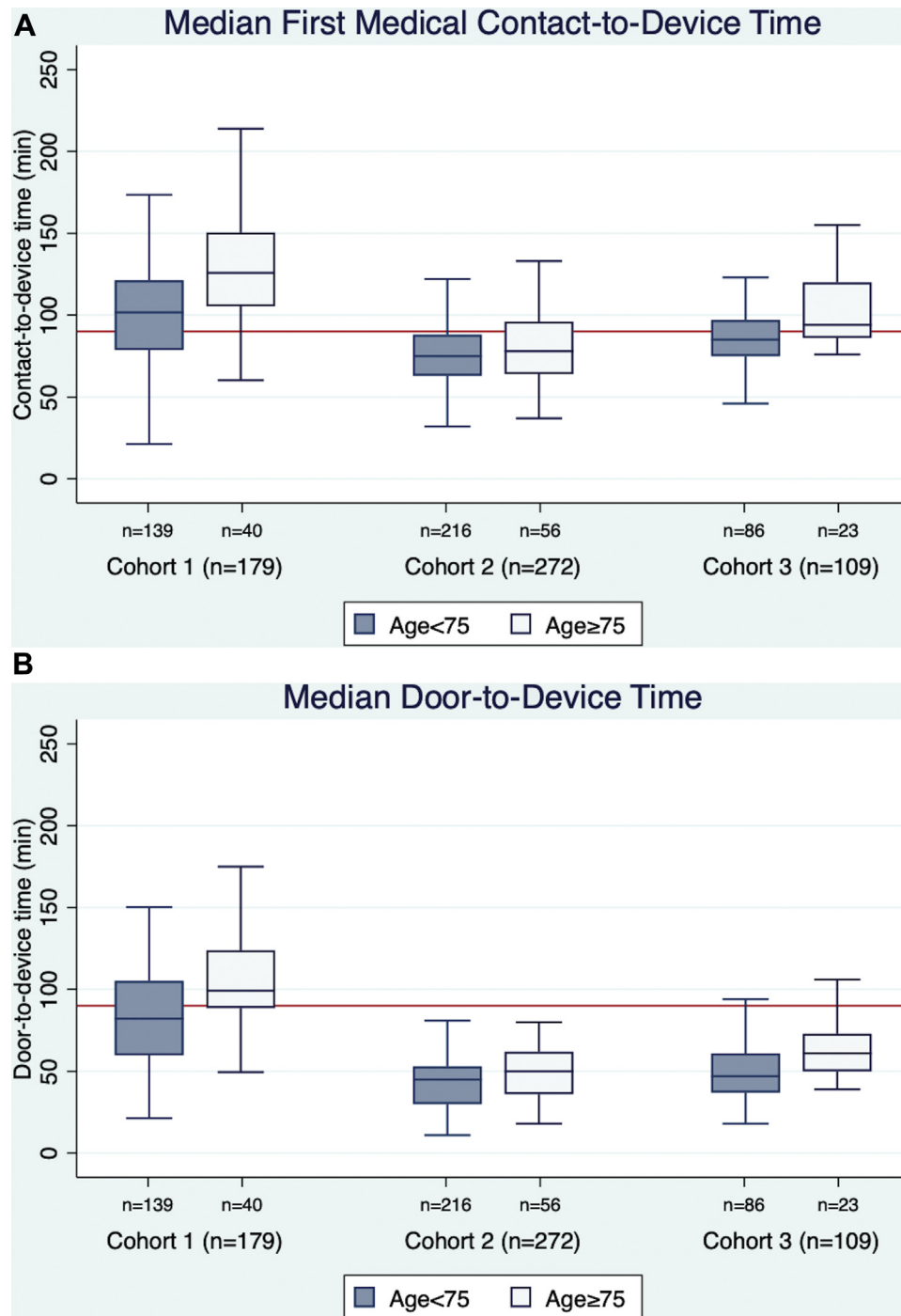Cohort 1 (n=179)   Cohort 2 (n=272)   Cohort 3 (n=109)

■ Women ■ Men

Figure 1. Median treatment delays according to sex by cohort. *Because of presence of extreme outliers, values are presented on a log scale. Cohort 1: Traditional hospital-based activation cohort. Cohort 2: An automated "physician-blind" prehospital activation cohort. Cohort 3: Prehospital activation with real-time physician oversight cohort.

$P = 0.08$; FMC-to-device: 92.5 [30] minutes vs 85 [20] minutes, $P = 0.06$). The elderly also experienced higher proportions of suboptimal TD (Table 3), and median TD was longer in those ≥ 75 of age, with a median FMC-to-device over 90 minutes (door-to-device: 61 [23] minutes vs 47 [24] minutes, $P < 0.01$; FMC-to-device: 94 [34] minutes vs 85 [22] minutes, $P < 0.01$).

When assessing multivariate predictors of suboptimal FMC-to-device in the prehospital CCL activation systems only (Table 4, Cohorts 2 and 3), female sex, history of CAD,

off-hours presentation, and physician oversight were independent predictors of suboptimal FMC-to-device times. Multivariate predictors of suboptimal treatment delay metrics across all 3 cohorts are shown in the Supplemental Table S1. Variance inflation factor analysis results were not suggestive of significant collinearity between sex and age group (< 10 for associations with either FMC-to-device or in-hospital mortality). There was no evidence of any interaction between sex and age group in their association with either suboptimal FMC-to-device times or mortality across all 3

Figure 2. Median treatment delays according to age group by cohort. *Because of presence of extreme outliers, values are presented on a log scale. Cohort 1: Traditional hospital-based activation cohort. Cohort 2: An automated "physician-blind" prehospital activation cohort. Cohort 3: Prehospital activation with real-time physician oversight cohort.

cohorts or when limited to only the prehospital activation cohorts (P = NS for all).

Because of immediate interhospital transfer of some patients following initial cardiac catheterization, data on in-hospital mortality were missing for 69 of 560 patients (12.3%) but did not appear to be nonrandom (Supplemental Tables S4 and S5). All-cause in-hospital mortality occurred in 31 of 491 patients for whom vital

status at discharge was available (6.3%). In prehospital cohorts, age ≥ 75, female sex, and Killip class III-IV were independently associated with mortality (P < 0.01, P = 0.04, and P < 0.01, respectively) (Table 5). Across all 3 cohorts, odds of in-hospital mortality were higher in women (odds ratio [OR] 2.31) but did not reach statistical significance (95% CI, 0.92-5.80, P = 0.07) (Supplemental Table S6).

Pacheco et al.
STEMI Activation Systems and Treatment Gaps

729

Table 3. Proportion of patients experiencing suboptimal treatment delays, according to sex and age group, by cohort

	Cohort 1 Hospital-based activation with physician oversight (Centre A) 2007-2009 (N = 179)			Cohort 2 Automated prehospital activation (Centre A) 2012-2014 (N = 272)			Cohort 3 Prehospital activation with physician oversight (Centre B) 2014-2015 (N = 109)		
	Women (N = 47)	Men (N = 132)	P value	Women (N = 78)	Men (N = 194)	P value	Women (N = 30)	Men (N = 79)	P value
Door-to-device > 90 min	28 (59.7%)	48 (36.4%)	< 0.01*	4 (5.1%)	5 (2.6%)	0.29	6 (20.0%)	2 (2.5%)	< 0.01*
FMC-to-device > 90 min	37 (78.7%)	78 (59.1%)	0.02*	25 (32.1%)	39 (20.1%)	0.04*	16 (53.3%)	26 (32.9%)	0.05
	< 75 yrs N = 139	≥ 75 yrs N = 40	P value	< 75 yrs N = 216	≥ 75 yrs N = 56	P value	< 75 yrs N = 86	≥ 75 yrs N = 23	P value
Door-to-device > 90 min	47 (33.8%)	29 (72.5%)	< 0.01*	7 (3.2%)	2 (3.6%)	0.90	5 (5.8%)	3 (13.0%)	0.23
FMC-to-device > 90 min	81 (58.3%)	34 (85.0%)	< 0.01*	47 (21.7%)	17 (30.4%)	0.18	29 (33.3%)	13 (56.5%)	0.05*

FMC, first medical contact.
* $P < 0.05$.

Discussion

Women and those patients older than 75 who presented with STEMI experienced longer TD in CCL activation systems with physician oversight, even if a prehospital activation system were in place. In contrast, an automated physician-blind prehospital activation system was associated with no difference in TD according to age and a reduced treatment gap for women. Overall, female sex and age ≥ 75 were independent predictors of suboptimal FMC-to-device times, as was physician oversight. Age ≥ 75, Killip class III or IV predicted in-hospital mortality, and there was a trend for an independent association with female sex.

To our knowledge, this is the first study examining the performance of STEMI diagnosis systems both with and without prehospital STEMI diagnosis and with and without physician oversight, according to sex and age. The observation that women and the elderly experience a higher proportion of suboptimal TD in cohorts with pre-CCL physician involvement but not in the cohort with a physician-blind prehospital CCL activation system not only supports that implicit systemic or provider bias may negatively affect system performance for these patients but also that automated systems that have previously been shown to have good diagnostic performance[19,20] may be a potential solution to treatment discrepancies in STEMI care.

In a study examining more than 100,000 patients with STEMI (including cases with prehospital ECG and ECG transmission), Roswell et al. reported higher median FMC-to-device times in women, with lower rates of prehospital ECG transmission for women compared with men transported by emergency medical services to hospital for STEMI.[2] Potential explanations for this include the persistent perception that cardiovascular disease is less frequent in women.[25] Women take longer to seek medical attention following onset of symptoms and,[8,9] possibly owing to sex differences in symptoms,[26,27] are less likely to be referred for invasive therapy[28,29] and have longer TD than men.[12] Pek et al. also reported longer treatment delays and lower referral for invasive therapy in patients diagnosed with STEMI aged older than 65.[5] As women are, on average, older than men when they present with acute myocardial infarction, the observed disparities in care may affect women disproportionately. The application of an automated physician-blind CCL activation protocol may help counter implicit biases in the evaluation of women and elderly patients with suspected STEMI and the unnecessary TDs that appear to result.

Improvement in TD with the implementation of a prehospital ECG,[30] as recommended by American Heart Association/American College of Cardiology (AHA/ACC) and Canadian Cardiovascular Society (CCS) STEMI guidelines,[23,31] and prehospital-based CCL activation protocol for suspected STEMI has been previously reported.[18,19] Importantly, the implementation of prehospital activation protocols is associated with shorter TD for both men and women. Huded

Table 4. Adjusted odds ratio of suboptimal FMC-to-device times across prehospital cardiac catheterization laboratory activation cohorts (2 and 3)

Variable	Univariate analysis OR (95% CI)	P value	Multivariate analysis OR (95% CI)	P value
Female sex	1.96 (1.21-3.16)	< 0.01	1.78 (1.05-3.00)	0.03*
Age ≥ 75 years	1.82 (1.08-3.07)	0.03	1.44 (0.81-2.55)	0.22
Smoking	1.20 (0.76-1.88)	0.43	-	-
Diabetes	0.90 (0.49-1.65)	0.74	-	-
HTN	1.16 (0.74-1.82)	0.51	-	-
DLP	1.14 (0.73-1.78)	0.57	-	-
History of CAD	2.27 (1.34-3.84)	< 0.01	2.34 (1.36-4.06)	< 0.01*
Off-hours presentation†	1.81 (1.11-2.95)	0.02	2.03 (1.21-3.39)	< 0.01*
Physician oversight	2.04 (1.27-3.28)	< 0.01	2.33 (1.41-3.85)	< 0.01*

CAD, coronary artery disease; DLP, dyslipidemia; HTN, hypertension; OR, odds ratio.
* Multivariate $P < 0.05$.
† Off-hours was defined as any case occurring outside of normal working hours (8 AM to 4 PM) for that centre, as well as weekends and holidays.

Table 5. Univariate and multivariate predictors of in-hospital mortality across prehospital cardiac catheterization laboratory activation cohorts (2 and 3)

Variable	Univariate analysis OR (CI₉₅)	P value	Multivariate analysis OR (95% CI)†	P value
Female sex	6.29 (2.49-15.88)	< 0.01	3.55 (1.06-11.84)	0.04*
Age ≥ 75 years	13.54 (5.09-36.06)	< 0.01	22.08 (5.39-90.42)	< 0.01*
Diabetes	0.98 (0.32-3.01)	0.98	-	-
Smoking	0.47 (0.19-1.18)	0.11	-	-
HTN	1.46 (0.61-3.48)	0.39	-	-
DLP	0.43 (0.18-1.05)	0.06	-	-
History of CAD	1.13 (0.40-3.17)	0.82	-	-
Killip class ≥ 3	16.99 (6.51-44.35)	< 0.01	34.37 (8.41-140.55)	< 0.01*
Physician oversight	1.64 (0.64-4.15)	0.30	-	-

The primary analysis excluded treatment delay variables (FMC-to-device and door-to-device) because they were on the putative causal pathway. The alternate analysis allowed these variables to assess the effect of female sex on the mortality bias not mediated by additional treatment delay.

CAD, coronary artery disease; DLP, dyslipidemia; FMC, first medical contact; HTN, hypertension; OR, odds ratio.

* Multivariate $P < 0.05$.

† Adjusted for female sex, age > 75, Killip class ≥ 3.

et al. reported a reduction in TD following the adoption of a 4-step STEMI care protocol, including direct emergency department CCL activation.[18] Door-to-device was reduced from 104 minutes to 89 minutes in men and from 112 minutes to 91 minutes in women ($P < 0.001$ for both). Similar findings have been reported by other regional STEMI referral systems.[17,32] We also observed shorter overall door-to-device and FMC-to-device times in both prehospital STEMI diagnosis cohorts compared with a traditional hospital-based CCL activation cohort. However, TD was lowest for women and those older than 75 years of age in the automated physician-blind system, suggesting that using an automated referral algorithm can successfully address persistent treatment shortfalls in certain subpopulations vulnerable to health care provider bias.

As previously reported,[4,5,29] age was an independent predictor of increased in-hospital mortality. There was a trend toward an independent association between suboptimal FMC-to-device times and increased in-hospital mortality, as would be expected,[2,11] and it appears likely that differences in FMC-to-device explains the signal for poorer in-hospital survival among women. As TD is perhaps the most reliable immediate objective measure of the impact of physician bias and, arguably, on the causal pathway between female sex and mortality, we elected to exclude FMC-to-device and door-to-device as candidate variables in the primary mortality model. That the inclusion of FMC-to-device in the explicative model (exploratory analysis; Supplemental Table S6 and S7) diminished the impact of female sex supports this hypothesis.

Standardized protocols for diagnosis, CCL activation, and initiation of pharmacologic management have previously been associated with a reduction in the observed mortality gap between women and men diagnosed with STEMI. Wei et al. reported similar 30-day mortality and 5-year mortality in both men and women following the implementation of a regional STEMI protocol in the greater Minneapolis area.[17] Huded et al. reported a decrease in the difference in 30-day all-cause mortality between men and women from 6.1% ($P = 0.002$) to 3.2% ($P = 0.090$) following the implementation of a 4-step protocol. The current study therefore reinforces these findings and adds that the use of automated algorithms might reduce treatment gaps and outcome discrepancies further. The incorporation of automated processes in medicine will likely increase with advances in artificial intelligence. However, the role of clinical expertise in overseeing the overall performance of such systems will remain. Automated systems may be optimized for flagging ECGs that required secondary validation by the on-duty physician while streamlining patients with straightforward ECGs to the CCL. Clinical assessment and expert judgement will be required at some point in the referral algorithm before catheterization. In our system, such an assessment was performed by the interventional cardiologist before proceeding with angiography. Importantly, we have shown previously that such a system can achieve low false positive and inappropriate activation rates by ECG criteria.[19,20] In addition, some patients were deemed inappropriate for emergent angiography on the basis of their comorbidities.

Limitations

The current study is a retrospective, nonrandomized analysis involving multiple cohorts and is subject to the inherent limitations of this type of data. Although some data were prospectively collected, other variables were abstracted from the medical record and may be subject to ascertainment bias. In addition, we compared data from 3 cohorts over different periods across 2 centres. However, other than the P2Y12-inhibitor of choice, all other aspects of management of STEMI did not change between the time periods, and both centres are staffed by the same group of interventional cardiologists, so differences in the STEMI referral systems among cohorts should be the primary driver of any variation in TD and in-hospital mortality. These data come from 2 "stand-alone" centres from a single metropolitan area and may not be representative of performance with or without real-time physician oversight in centres with cardiac surgery on site or in other metropolitan areas. The geographic area served by each centre is also necessarily different, which could confound the observed association between physician oversight and TD. However, as the geographic STEMI catchment area for each centre was determined to ensure optimal TD for all patients, measuring the rate of optimal TD among the subpopulations of interest in each cohort (instead of TD as a continuous variable) should minimize the impact of geographic disparities. Moreover, multivariate predictors of suboptimal TD were derived using all cohorts and therefore across all

Pacheco et al.
STEMI Activation Systems and Treatment Gaps

731

geographies. In-hospital mortality data were missing in 12.3% of cases, and long-term mortality data were unavailable. As the rate of missing data was similar among women and men and the elderly and nonelderly, we elected not to impute missing in-hospital mortality data.

Conclusions

Real-time physician involvement in STEMI-activation protocols, whether hospital-based or prehospital, are associated with significant TD disparities for women and the elderly, who are also at an increased risk of in-hospital death. Automated physician-blind STEMI activation, on the other hand, was not associated with any significant difference in TD according to age and a smaller TD gap between women and men. The reduced TD gap observed for women and older patients with a physician-blind system suggests that physician or other provider bias in the diagnosis and referral of patients with STEMI can negatively affect care, even when prehospital activation systems are in place. Additional studies, including multicentric regional data and randomized controlled trials comparing automated and traditional referral systems, are needed to confirm these hypothesis-generating findings. Addressing these biases and treatment discrepancies represent important avenues for improvement of quality of care, and specific reporting of system performance for at-risk groups should be encouraged.

Acknowledgements

The authors would like to acknowledge the work of the clinical teams who help to maintain the prospective STEMI database at both centres.

Funding Sources

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: a scientific statement from the American Heart Association. Circulation 2016;133:916-47.

2. Roswell RO, Kunkes J, Chen AY, et al. Impact of sex and contact-to-device time on clinical outcomes in acute ST-segment elevation myocardial infarction-findings from the National Cardiovascular Data registry. J Am Heart Assoc 2017;6:e004521.

3. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J, Zaman S. Sex Differences persist in time to presentation, revascularization, and mortality in myocardial infarction treated with percutaneous coronary intervention. J Am Heart Assoc 2019;8:e012161.

4. Pancholy SB, Shantha GP, Patel T, Cheskin LJ. Sex differences in short-term and long-term all-cause mortality among patients with ST-segment elevation myocardial infarction treated by primary percutaneous intervention: a meta-analysis. JAMA Intern Med 2014;174:1822-30.

5. Pek PP, Zheng H, Ho AFW, et al. Comparison of epidemiology, treatments and outcomes of ST segment elevation myocardial infarction between young and elderly patients. Emerg Med J 2018;35:289-96.

6. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. JAMA 2012;307:813-22.

7. Khan NA, Daskalopoulou SS, Karp I, et al. Sex differences in acute coronary syndrome symptom presentation in young patients. JAMA Intern Med 2013;173:1863-71.

8. Benamer H, Bataille S, Tafflet M, et al. Longer pre-hospital delays and higher mortality in women with STEMI: the e-MUST registry. EuroIntervention 2016;12:e542-9.

9. Sederholm Lawesson S, Isaksson RM, Ericsson M, Angerud K, Thylen I; SymTime Study Group. Gender disparities in first medical contact and delay in ST-elevation myocardial infarction: a prospective multicentre Swedish survey study. BMJ Open 2018;8:e020211.

10. Chang AM, Mumma B, Sease KL, Robey JL, Shofer FS, Hollander JE. Gender bias in cardiovascular testing persists after adjustment for presenting characteristics and cardiac risk. Acad Emerg Med 2007;14:599-605.

11. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol 2006;47:2180-6.

12. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. Am Heart J 2011;161:91-7.

13. Choi K, Shofer FS, Mills AM. Sex differences in STEMI activation for patients presenting to the ED 1939. Am J Emerg Med 2016;34:1939-43.

14. Diercks DB, Kontos MC, Chen AY, et al. Utilization and impact of pre-hospital electrocardiograms for patients with acute ST-segment elevation myocardial infarction: data from the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry. J Am Coll Cardiol 2009;53:161-6.

15. Rokos IC, French WJ, Koenig WJ, et al. Integration of pre-hospital electrocardiograms and ST-elevation myocardial infarction receiving center (SRC) networks: impact on door-to-balloon times across 10 independent regions. JACC Cardiovasc Interv 2009;2:339-46.

16. Cantor WJ, Hoogeveen P, Robert A, et al. Prehospital diagnosis and triage of ST-elevation myocardial infarction by paramedics without advanced care training. Am Heart J 2012;164:201-6.

17. Wei J, Cheng Y, Guo WH, et al. Molecular diversity and potential anti-neuroinflammatory activities of cyathane diterpenoids from the basidiomycete cyathus Africanus. Sci Rep 2017;7:8883.

18. Huded CP, Johnson M, Kravitz K, et al. 4-Step protocol for disparities in STEMI care and outcomes in women. J Am Coll Cardiol 2018;71:2122-32.

19. Potter BJ, Matteau A, Mansour S, et al. Sustained performance of a "physicianless" system of automated pre-hospital STEMI diagnosis and catheterization laboratory activation. Can J Cardiol 2017;33:148-54.

20. Potter BJ, Matteau A, Mansour S, et al. Performance of a new "physicianless" automated system of prehospital ST-segment elevation myocardial infarction diagnosis and catheterization laboratory activation. Am J Cardiol 2013;112:156-61.

21. Québec Idlsd. Institut de la statistique du Québec, http://www.stat.gouv.qc.ca/statistiques/profils/region_13/region_13_00.htm. Accessed September 17, 2018.

22. Québec Indlsd, http://www.stat.gouv.qc.ca/statistiques/profils/region_1 6/region_16_00.htm. Accessed September 17, 2018.

23. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv 2013;82:E1-27.

24. Miles J. Tolerance and variance inflation factor. Wiley StatsRef: Statistics Reference Online, 2014.

25. Wenger NK. You've come a long way, baby: cardiovascular health and disease in women: problems and prospects. Circulation 2004;109:558-60.

26. Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation 2018;137:781-90.

27. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006;47(suppl 3):S21-9.

28. Skelding KA, Boga G, Sartorius J, et al. Frequency of coronary angiography and revascularization among men and women with myocardial infarction and their relationship to mortality at one year: an analysis of the Geisinger myocardial infarction cohort. J Interv Cardiol 2013;26: 14-21.

29. Alabas OA, Gale CP, Hall M, et al. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: national cohort study using the SWEDEHEART registry. J Am Heart Assoc 2017;6:e007123.

30. Gupta A, Barrabes JA, Strait K, et al. Sex differences in timeliness of reperfusion in young patients with ST-segment-elevation myocardial infarction by initial electrocardiographic characteristics. J Am Heart Assoc 2018;7:e007021.

31. Wong GC, Welsford M, Ainsworth C, et al. 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology guidelines on the acute management of ST-elevation myocardial infarction: focused update on regionalization and reperfusion. Can J Cardiol 2019;35:107-32.

32. Glickman SW, Granger CB, Ou FS, et al. Impact of a statewide ST-segment-elevation myocardial infarction regionalization program on treatment times for women, minorities, and the elderly. Circ Cardiovasc Qual Outcomes 2010;3:514-21.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.01.009.