






ORIGINAL RESEARCH

Predictors of the Use of Mineralocorticoid Receptor Antagonists in Patients With Left Ventricular Dysfunction Post-ST-Segment–Elevation Myocardial Infarction

Eric C. Wong, BSc(Pharm), ACPR, MD; Christopher B. Fordyce, MD, MHS, MSc; Graham Wong, MD, MPH; Terry Lee , PhD; Michele Perry-Arnesen , MHA, BSN, RN; Martha Mackay, PhD, RN, CCN(C); Joel Singer , PhD; John A. Cairns , MD; Ricky D. Turgeon , BSc(Pharm), ACPR, PharmD

BACKGROUND: Guidelines recommend mineralocorticoid receptor antagonist (MRA) use in patients with left ventricular ejection fraction $\leq 40\%$ following a myocardial infarction plus heart failure or diabetes mellitus, based on mortality benefit in the EPHEBUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial. The objective of this study was to evaluate the real-world utilization of MRAs for patients with ST-segment–elevation myocardial infarction (STEMI) with left ventricular dysfunction.

METHODS AND RESULTS: The prospective, population-based, Vancouver Coastal Health Authority STEMI database was linked with local outpatient cardiology records from 2007 to 2018. EPHEBUS criteria were used to define post-STEMI MRA eligibility (left ventricular ejection fraction $\leq 40\%$ plus clinical heart failure or diabetes mellitus, and no dialysis-dependent renal dysfunction). The primary outcome was MRA prescription among eligible patients at discharge and the secondary outcome was MRA prescription within 3 months postdischarge. Of 2691 patients with STEMI, 317 (12%) were MRA eligible, and 70 (22%) eligible patients were prescribed an MRA at discharge. Among eligible patients with no MRA at discharge, 12/126 (9.5%) with documented postdischarge follow-up were prescribed an MRA within 3 months. In multivariable analysis, left ventricular ejection fraction (odds ratio [OR], 1.55 per 5% left ventricular ejection fraction decrease; 95% CI, 1.26–1.90) and calendar year (OR, 1.23 per year, 95% CI, 1.11–1.37) were associated with MRA prescription at discharge. Other prespecified variables were not associated with MRA prescription.

CONCLUSIONS: In this contemporary STEMI cohort, only 1 in 4 MRA-eligible patients were prescribed an MRA within 3 months following hospitalization despite high-quality evidence for use. Novel decision-support tools are required to optimize pharmacotherapy decisions during hospitalization and follow-up to target this gap in post-STEMI care.

Key Words: acute coronary syndrome ■ aldosterone antagonist ■ heart failure

Left ventricular (LV) dysfunction, with or without overt clinical heart failure (HF), occurs in ≈ 1 in 4 patients hospitalized for myocardial infarction (MI), and is associated with worse clinical outcomes.^{1,2} Specifically, LV

dysfunction is associated with higher mortality, including early all-cause mortality and sudden cardiac death.³ Since 2004, guidelines have recommended the use of a mineralocorticoid receptor antagonist (MRA) in eligible

See Editorial by Schupp et al.

Correspondence to: Ricky D. Turgeon, BSc(Pharm), ACPR, PharmD, University of British Columbia, 2405 Wesbrook Mall, Vancouver, British Columbia, Canada V6T 1Z3. E-mail: ricky.turgeon@ubc.ca

Supplementary Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.019167>

For Sources of Funding and Disclosures, see page 9.

© 2021 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Only 1 in 4 patients with left ventricular dysfunction following ST-segment–elevation myocardial infarction who meet EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial criteria receive a mineralocorticoid receptor antagonist within 3 months of ST-segment–elevation myocardial infarction discharge.

What Are the Clinical Implications?

- These findings support the need for novel decision-support tools to facilitate uptake and optimization of mineralocorticoid receptor antagonists and other evidence-based pharmacotherapy options during ST-segment–elevation myocardial infarction and at follow-up appointments.

Nonstandard Abbreviations and Acronyms

ACTION-GWTG	Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines
EPHEsus	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
MRA	mineralocorticoid receptor antagonist

patients who are post-MI, based on the inclusion criteria of the EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial.^{4–6} The EPHEsus trial demonstrated that, compared with placebo, an MRA started 3 to 14 days after hospital admission for acute MI reduced mortality in patients with LV dysfunction (LV ejection fraction [LVEF] \leq 40%) and either clinical HF or diabetes mellitus.⁷ Importantly, this benefit occurred rapidly, with a significant reduction in 30-day mortality,⁸ and was greatest when started early, with a 31% relative risk reduction in mortality when eplerenone was initiated 3 to 6 days post-MI compared with a nonsignificant 6% reduction when initiated 7 to 14 days post-MI.⁹ These findings were supported by mechanistic research demonstrating that MRAs reduce early myocardial remodeling and fibrosis after MI.^{10,11} Therefore, the benefits of an MRA post-MI may be time sensitive, and delayed initiation beyond 1 week may represent a missed opportunity to improve patient outcomes.

Despite the benefits of MRAs in patients with post-MI LV dysfunction, use of these agents in clinical

practice remains highly variable.¹² In the US-based National Cardiovascular Data Registry ACTION-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry–Get With the Guidelines) study from 2007 to 2011, only 14.5% of MRA-eligible patients received an MRA at discharge,¹ whereas use among eligible patients was 54.8% in a Spanish study from 2006 to 2008.¹³ Neither study showed a trend for increased adoption of MRA use over time, although MRA uptake may have been low because of the short duration of both studies and the short interval from publication of EPHEsus to each study. Furthermore, no study has specifically evaluated the initiation of MRA after discharge among patients with MI with LV dysfunction. Although the benefit of MRAs occurs early after MI, clinicians may choose not to prescribe an MRA during admission with the aim of titrating other MI therapies and initiating an MRA on follow-up, which would not be captured by evaluating discharge prescriptions only.

We analyzed a population-based cohort of consecutive patients with ST-segment–elevation MI (STEMI) with LV dysfunction from the Vancouver Coastal Health Authority STEMI database to determine the proportion of eligible patients with STEMI prescribed an MRA at discharge and within 3 months after hospitalization. Among MRA-eligible patients, we sought to identify predictors and evaluate the contemporary frequency and temporal trends in MRA utilization.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results.

Experimental Design and Data Sources

We analyzed data from the Vancouver Coastal Health STEMI database, a prospective, population-based study of all patients with STEMI treated at 1 of the 13 hospitals within the Vancouver Coastal Health region, which includes 2 percutaneous coronary intervention–capable quaternary-care centers.^{14,15} We linked the Vancouver Coastal Health STEMI database with local postdischarge outpatient cardiology encounters within the iClinic electronic medical record. We included all patients \geq 18 years of age who were admitted for STEMI, managed with revascularization by primary percutaneous coronary intervention or fibrinolysis, and discharged from the hospital alive between June 26, 2007 and March 31, 2018. We excluded patients who had presented with out-of-hospital cardiac arrest, or had data missing on LVEF, diabetes mellitus status, or medications prescribed at discharge.

Outcomes

The primary outcome was the proportion of eligible patients with STEMI who were prescribed an MRA at discharge. The secondary outcome was the proportion of eligible patients with STEMI not prescribed an MRA at discharge who were subsequently prescribed an MRA within 3 months postdischarge. We defined MRA eligibility based on the EPHEMUS trial inclusion criteria: LVEF $\leq 40\%$ (based on the last evaluation by contrast ventriculography, echocardiography, or cardiac magnetic resonance imaging performed during the admission), plus either clinical HF (including HF on presentation or during hospitalization) or prior history of diabetes mellitus, and without dialysis-dependent renal dysfunction.

Statistical Analysis

We reported continuous variables as means with SDs or medians with interquartile range for descriptive statistics, and categorical values as proportions using percentages (%). We performed univariate comparisons of characteristics between patients prescribed an MRA at discharge to those without MRA prescription at discharge using the Student's *t* test or Wilcoxon rank sum test for continuous variables and the χ^2 test or Fisher exact test for categorical variables as appropriate. Additionally, we evaluated time trends in MRA prescription by comparing the proportion of MRA-eligible patients with STEMI with MRA prescription at discharge by calendar year, and evaluated this trend using the Cochran-Armitage test.

For the primary analysis evaluating variables associated with MRA prescription at discharge, we used multivariable logistic regression to calculate odds ratios (OR) and 95% CIs for a prespecified list of candidate variables available during the index admission. These candidate variables included calendar year, age, sex, anterior MI, hospital length-of-stay (as a continuous variable), LVEF (as a continuous variable), presentation to a percutaneous coronary intervention-capable hospital, calendar year, and angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use within 24 hours of presentation.

For the secondary analysis evaluating variables associated with postdischarge MRA prescription among patients not prescribed an MRA at discharge, we used univariate analysis (χ^2 , Fisher exact, or Wilcoxon rank sum tests, as appropriate) for a list of candidate variables available during the follow-up visit, including a modified congestion score¹⁶ (range 0–3 based on presence of jugular venous pressure elevation, crackles, and peripheral edema), serum creatinine, serum potassium, and LVEF on postdischarge imaging.

All analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC). The threshold for statistical significance for all analyses was set at a 2-sided $P < 0.05$. One author (T.L.) had full access to all the data in the study and takes

responsibility for its integrity and the data analysis. This study was approved by the Clinical Research Ethics Board of the University of British Columbia and the requirement for patient consent was waived.

RESULTS

Cohort Characteristics

From June 26, 2007 to March 31, 2018, a total of 2691 patients with STEMI met our inclusion criteria (Figure 1). Of these, 317 (11.8%) were eligible for an MRA based on the EPHEMUS trial criteria. The mean age of MRA-eligible patients was 67 years, 22% were female, and 78% presented with an anterior MI. Mean LVEF was 33% ($\pm 7\%$), 48% had diabetes mellitus, and 69% had clinical HF (first documented on presentation in 19% and subsequently in the hospital in 50%) (Table 1).

Prescription of MRA at Discharge

In total, 70 (22.0%) of MRA-eligible patients received an MRA prescription at discharge. In univariate analysis, lower LVEF, lower prevalence of diabetes mellitus, HF in the hospital, prior percutaneous coronary intervention, and in-hospital cardiac arrest were significantly associated with MRA discharge prescription (Table 1). Additionally, use of an MRA or enoxaparin within 24 hours of presentation and discharge prescription for warfarin, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and optimal medical therapy were each associated with MRA prescription (Table 1). When considering MRA use based on calendar year, there was a significant trend for increased MRA prescription at discharge among MRA-eligible patients over time ($P < 0.001$) (Figure 2).

In the prespecified multivariable analysis, LVEF (OR, 1.55 per 5% LVEF decrease; 95% CI, 1.26–1.90; $P < 0.001$) and calendar year (OR, 1.23 per year increase, 95% CI, 1.11–1.37, $P < 0.001$) were independently associated with MRA prescription (Table 2). Patients with a LVEF 31% to 40% comprised the majority of MRA-eligible patients not receiving an MRA at discharge (Figure 3). No other candidate variable was associated with MRA prescription at discharge. In post hoc multivariable analysis adding history of diabetes mellitus and peak creatinine to the model, LVEF and calendar year remained independently associated with MRA prescription at discharge (Table S1). Similar patterns emerged in subgroup analysis of patients with diabetes mellitus (Table S2).

Prescription of MRA Within 3 Months After Discharge

Of the remaining 247 MRA-eligible patients with STEMI who were not prescribed an MRA at discharge, 126

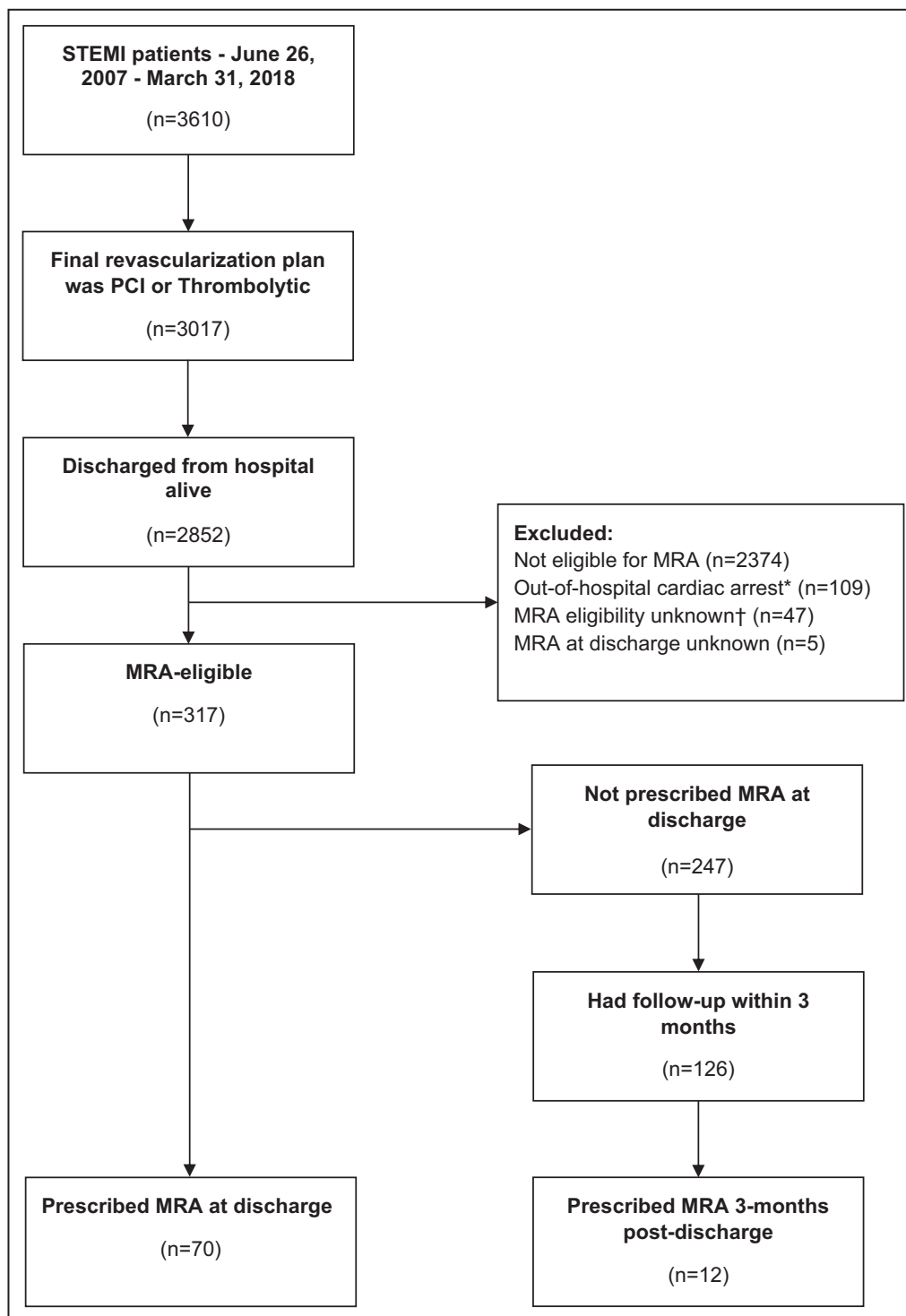


Figure 1. Cohort derivation.

*Status systematically collected from 2012 onward. Participants with unknown status were included in the analysis. †Missing data for left ventricular ejection fraction, clinical heart failure, diabetes mellitus, and/or dialysis. MRA indicates mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

(51%) had a documented cardiology follow-up within 3 months, of whom 12 (9.5%) were prescribed an MRA. Among patients who had local cardiology follow-up

within 3 months, the median time from discharge to first cardiology follow-up was 53 days (interquartile range, 36–70). In univariate analysis, patients who were

Table 1. Characteristics of MRA-Eligible Patients With STEMI

Characteristic	Total MRA-Eligible (n=317)	No MRA at Discharge (n=247)	MRA at Discharge (n=70)	P Value
Age, mean (SD), y	67.4 (12.9)	67.9 (12.9)	65.7 (12.5)	0.214
Female patients, n (%)	68 (21.5)	55 (22.3)	13 (18.6)	0.506
BMI, mean (SD)	27.0 (5.2)	26.8 (5.2)	27.8 (5.0)	0.165
STEMI admission details				
Anterior infarct, n (%)	248 (78.2)	193 (78.1)	55 (78.6)	0.938
HF on presentation, n (%)	59 (18.6)	49 (19.8)	10 (14.3)	0.292
Admitted to PCI-capable hospital, n (%)	216 (68.1)	172 (69.6)	44 (62.9)	0.283
PCI, n (%)	310 (97.8)	241 (97.6)	69 (98.6)	0.615
Fibrinolysis only, n (%)	7 (2.2)	6 (2.4)	1 (1.4)	0.615
In-hospital HF, n (%)	207 (65.3)	151 (61.1)	56 (80.0)	0.003
In-hospital cardiac arrest, n (%)	23 (12.9)	12 (9.3)	11 (22.4)	0.020
Unknown, n	139	118	21	
Hospital length-of-stay, median (IQR), d	4.7 (3.2–8.3)	4.5 (3.2–8.2)	5.4 (3.3–9.8)	0.593
≤3 d, n (%)	64 (20.2)	51 (20.6)	13 (18.6)	0.702
Cardiovascular disease and risk factors, n (%)				
Diabetes mellitus	151 (47.6)	127 (51.4)	24 (34.3)	0.011
Prior HF	18 (5.7)	12 (4.9)	6 (8.6)	0.236
Prior MI	72 (22.7)	54 (21.9)	18 (25.7)	0.497
Prior PCI	48 (15.1)	32 (13.0)	16 (22.9)	0.041
Current/recent smoker	69 (21.8)	54 (21.9)	15 (21.4)	0.938
Hypertension	211 (66.6)	164 (66.4)	47 (67.1)	0.907
Dyslipidemia	157 (49.5)	122 (49.4)	35 (50.0)	0.929
Clinical and laboratory values				
LVEF				
Mean (SD)	32.6 (6.6)	33.4 (6.4)	29.5 (6.5)	<0.001
Median (IQR)	35 (30–38)	35 (30–40)	30 (25–35)	
≤20%, n (%)	38 (12.0)	24 (9.7)	14 (20.0)	0.019
Admission heart rate, mean (SD), bpm	87.7 (26.2)	88.0 (26.1)	86.7 (27.0)	0.711
Admission SBP, mean (SD), mm Hg	137.6 (31.8)	138.1 (30.8)	135.8 (35.4)	0.599
Admission hemoglobin, mean (SD), g/L	140.7 (18.6)	140.3 (18.5)	142.1 (18.9)	0.475
Admission creatinine, median (IQR), μmol/L	97 (81–113)	97 (79–114)	97 (86–110)	0.454
Peak creatinine, median (IQR), μmol/L	109 (92–137)	110 (90–140)	107.5 (96–133)	0.948
Medications within 24 h of admission, n (%)				
Aspirin	314 (99.1)	244 (98.8)	70 (100.0)	1.000
P2Y ₁₂ inhibitor	309 (97.5)	239 (96.8)	70 (100.0)	0.127
Enoxaparin	105 (33.1)	75 (30.4)	30 (42.9)	0.050
Statin	306 (96.5)	238 (96.4)	68 (97.1)	0.751
ACEI/ARB	258 (81.4)	205 (83.0)	53 (75.7)	0.167
β-blocker	266 (83.9)	212 (85.8)	54 (77.1)	0.081
MRA	8 (2.5)	0 (0.0)	8 (11.4)	<0.001

(Continued)

Table 1. (Continued)

Characteristic	Total MRA-Eligible (n=317)	No MRA at Discharge (n=247)	MRA at Discharge (n=70)	P Value
Medications at discharge, n (%)				
Aspirin	311 (98.1)	243 (98.4)	68 (97.1)	0.617
P2Y ₁₂ inhibitor	302 (95.3)	234 (94.7)	68 (97.1)	0.403
Warfarin	135 (42.6)	115 (46.6)	20 (28.6)	0.007
Statin	316 (99.7)	246 (99.6)	70 (100.0)	1.000
ACEI/ARB	280 (88.3)	211 (85.4)	69 (98.6)	0.002
β-blocker	311 (98.1)	241 (97.6)	70 (100.0)	0.345
Optimal medical therapy [†]	263 (83.0)	197 (79.8)	66 (94.3)	0.004

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; bpm, beats per minute; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and STEMI, ST-segment–elevation myocardial infarction.

[†]Defined as use of the combination of aspirin plus P2Y₁₂ inhibitor plus ACEI/ARB plus β-blocker.

prescribed an MRA at postdischarge follow-up had lower LVEF on postdischarge cardiac imaging (median LVEF 32.5%) than those not prescribed an MRA postdischarge (median LVEF 40%, *P*=0.042; Table 3). Other candidate variables were not associated with MRA prescription postdischarge. Overall, a cumulative 82/317 (25.9%) MRA-eligible patients were prescribed an MRA within 3 months after discharge from STEMI hospitalization.

DISCUSSION

In this contemporary cohort of patients with STEMI, ≈12% had MRA-eligible LV dysfunction according to the EPHEBUS trial criteria, yet only 1 in 4

MRA-eligible patients were prescribed an MRA within 3 months after hospitalization, despite high-quality evidence of early mortality benefit.⁷ MRA use increased significantly over the 11-year timeframe of our study, suggesting increased adherence to guideline recommendations over time. Lower LVEF was the only independent clinical predictor of MRA prescription at discharge and follow-up among MRA-eligible patients; no other patient-level variables were independently associated with MRA prescription. The relatively infrequent prescription of MRA to eligible patients highlights an important gap between evidence-based guidelines and current treatment patterns for patients with acute MI, which has lessened over time.

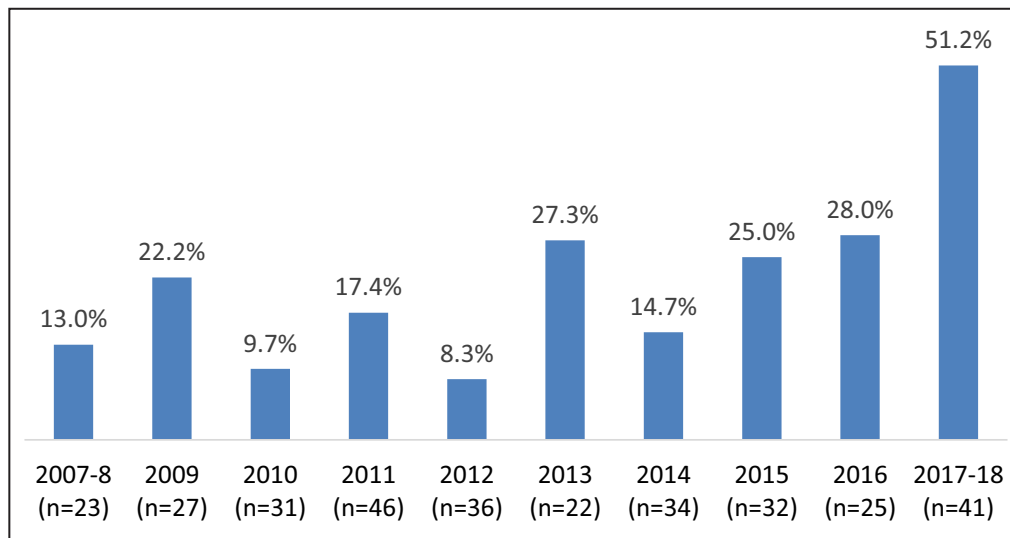


Figure 2. Proportion of MRA-eligible patients with STEMI* with MRA prescription at discharge by calendar year*†.

*MRA-eligible patients with STEMI: Left ventricular ejection fraction ≤40% plus either clinical heart failure or prior history of diabetes mellitus, and without dialysis-dependent renal dysfunction. †n denotes the number of MRA-eligible patients with STEMI in that year. MRA indicates mineralocorticoid receptor antagonist; and STEMI, ST-segment–elevation myocardial infarction.

Table 2. Association Between Candidate Variables and MRA Prescription at Discharge Among MRA-Eligible Patients With STEMI

	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	P Value
LVEF (per 5% decrease)	1.53 (1.26–1.87)	1.55 (1.26–1.90)	<0.001
Calendar year (per year increase)	1.22 (1.10–1.35)	1.23 (1.11–1.37)	<0.001
Age, per 10-y decrease	1.14 (0.93–1.40)	1.14 (0.90–1.44)	0.278
Male patients	1.23 (0.63–2.39)	1.21 (0.57–2.56)	0.614
Nonanterior location	0.99 (0.52–1.88)	1.06 (0.53–2.12)	0.863
Non-PCI-capable hospital	1.36 (0.78–2.37)	1.41 (0.78–2.57)	0.256
Hospital length-of-stay, per day increase	1.00 (0.98–1.02)	1.00 (0.98–1.02)	0.976
No ACEI/ARB use within 24 h of presentation	1.58 (0.84–2.99)	1.38 (0.69–2.76)	0.367

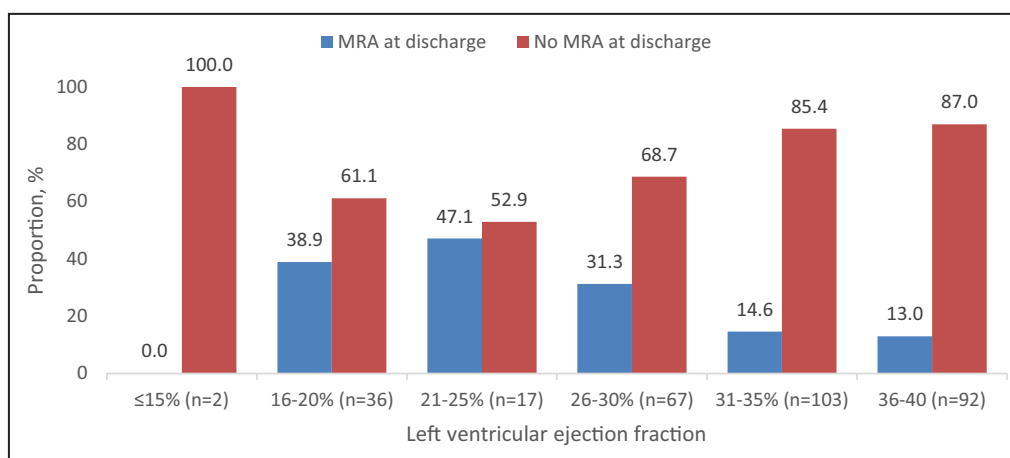
ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation myocardial infarction.

*Multivariable adjustment for other covariates listed in this table.

We extend the results of the ACTION-GWTG data set from the United States, in which only 14.5% of MRA-eligible patients with STEMI were prescribed an MRA at discharge, by assessing for delayed MRA initiation postdischarge.¹ Our results demonstrate that MRAs are infrequently prescribed among eligible patients after STEMI discharge. This is consistent with the under-use of MRAs among outpatients with chronic HF with reduced ejection fraction, in which only \approx 1 in 3 eligible patients with HF with reduced ejection fraction receive an MRA.^{17,18} Initiation of MRAs among eligible patients during their STEMI admission therefore represents an opportunity to

maximize early benefits and increase the likelihood of outpatient use. Unlike ACTION-GWTG, we found a significant improvement in MRA prescription at discharge over time, which may reflect the longer available timeframe and more recent data available within our database. Our study further confirms the observation from ACTION-GWTG that patients meeting the EPHEBUS criterion on the basis of having diabetes mellitus without overt HF are less likely to be prescribed an MRA.^{4,6} In our study, patients with LV dysfunction and diabetes mellitus without clinical HF accounted for nearly one third of MRA-eligible patients. Therefore, this subgroup of patients with diabetes mellitus and American College of Cardiology/American Heart Association stage B HF represents a target subgroup for quality improvement initiatives targeting the MRA treatment gap. Furthermore, in the present study, patients with lower LVEF were associated with a higher likelihood of being prescribed an MRA, likely reflecting prescribers' impression of the benefit-harm assessment based on patient prognosis. However, there was a mortality benefit across the LVEF range studied in the EPHEBUS trial.^{7,19} This highlights that clinicians caring for patients post-MI with LV dysfunction should consider therapy even among patients with only "mildly" reduced LVEF.

Several patient factors may be perceived as barriers to early initiation of MRAs during the initial STEMI hospitalization, such as hypotension, renal dysfunction, or hyperkalemia.^{1,7,12} A recent analysis of the RALES (Randomized Aldactone Evaluation Study) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) trials demonstrated a minimal effect of MRAs on blood pressure in patients with HF with reduced ejection fraction with systolic blood pressure \leq 105 mm Hg at

**Figure 3. Distribution of MRA-eligible patients with STEMI by left ventricular ejection fraction and MRA prescription at discharge.**

MRA indicates mineralocorticoid receptor antagonist; and STEMI, ST-segment-elevation myocardial infarction.

Table 3. Association Between MRA Prescription Within 3 Months and Selected Variables Among 126 MRA-Eligible Patients With STEMI Not Prescribed an MRA at Discharge

	No MRA (n=114)	MRA (n=12)	P Value
LVEF, median (IQR), %	40.0 (35.0–49.0) n=43	32.5 (30.0–33.0) n=5	0.042
Modified congestion score [†] , n (%)			0.289
0	92 (80.7)	10 (83.3)	
1	16 (14.0)	1 (8.3)	
2	5 (4.4)	0	
3	1 (0.9)	1 (8.3)	
Serum potassium			
Median (IQR), mmol/L	4.4 (4.1–4.7) n=35	3.5 (–) n=1	0.091
>5.5 mmol/L	n=0	n=0	...
Serum creatinine, median (IQR), μmol/L	94.0 (82.0–118.0) n=39	99.5 (87.0–112.0) n=2	1.000

IQR indicates interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; and STEMI, ST-segment-elevation myocardial infarction.

[†] Range 0 to 3 based on presence of jugular venous pressure elevation, crackles, and peripheral edema.

baseline, indicating that the presence of asymptomatic hypotension alone should not lead to the decision to withhold MRA therapy.²⁰ Furthermore, while renal dysfunction and hyperkalemia are certainly important considerations before starting an MRA, they can be mitigated by ensuring early postdischarge follow-up with repeat bloodwork. In practice, clinicians may elect to delay MRA initiation until renin-angiotensin system blockers and β -blockers are optimized,¹⁸ thereby missing an opportunity to add a therapy that reduces mortality during the period of highest risk.

Quality improvement efforts are required to further optimize guideline-directed post-STEMI therapy decisions. For example, improved strategies in prescriber education regarding the indications for MRAs in post-MI LV dysfunction beyond its use in chronic HF with reduced ejection fraction may improve its overall appropriate utilization. Current routine practices of clinician education through institutional cardiology rounds or academic detailing programs may, however, have limited long-term efficacy in meaningfully overcoming prescribing inertia.^{21,22} Therefore, other strategies should also be explored, such as an expanded role for clinical pharmacists to initiate post-MI therapy based upon standardized clinical criteria.^{23,24} Furthermore, decision-support tools may be developed to improve use of evidence-based therapies before discharge. For example, automated

point-of-care alerts in the context of integrated electronic medical records can prompt a clinician to prescribe an MRA based upon a patient's date of index STEMI, LVEF on imaging, and current list of post-MI therapies. Similar strategies of automated evidence-based electronic medical record alerts among patients with HF have shown increased use of optimal medical therapy in that population.²⁵

Strengths and Limitations

The major strength of this study is the inclusion of consecutive patients with STEMI managed within a regional network of hospitals over an 11-year timeframe, using standardized data collection tools. Nevertheless, this study should also be interpreted in the context of some limitations. First, our data set did not include documentation of loop diuretic use, in-hospital serum potassium, or all blood pressure or serum creatinine measurements, and reasons for not prescribing an MRA may not have been documented during clinical encounters. Therefore, a subset of MRA-eligible patients may have had a valid contraindication to therapy that we could not ascertain, though only 8.6% patients in the ACTION-GWTG had a contraindication to an MRA.¹ Second, when abstracting data into the database, the lower end of a reported LVEF range was used. This may have led to some patients with "mid-range" LVEF (eg, 40%–45%), outside the EPHEBUS eligibility criteria, to be classified as MRA eligible. Despite this, MRA use was low among all LVEF categories, particularly within patients with LVEF 31% to 35%. Finally, among patients without an MRA prescribed at discharge, post-discharge MRA use could only be assessed in the 51% who had local cardiology follow-up documented within the iClinic electronic medical record, and patients who received follow-up in another health region were not captured. However, we anticipate that MRA use would be similar or lower than the group with close cardiology follow-up.

CONCLUSIONS

In our contemporary regional STEMI cohort, only 1 in 4 MRA-eligible patients were prescribed an MRA within 3 months following hospitalization, despite high-quality evidence that early use reduces mortality. Aside from lower LVEF and calendar year, MRA utilization was not associated with any patient- or institutional-level characteristics, suggesting unexplained variability in clinical practice. Novel decision-support tools are required to optimize guideline-directed therapy decisions during hospitalization and follow-up to target this gap in post-STEMI care.

ARTICLE INFORMATION

Received November 17, 2020; accepted March 22, 2021.

Affiliations

Division of General Internal Medicine, Department of Medicine (E.C.W.); Division of Cardiology, Department of Medicine (C.B.F., G.W., J.A.C., R.D.T.); and Centre for Health Evaluation and Outcome Sciences, Providence Health Care Research Institute (C.B.F., T.L., M.M., J.S., R.D.T.), University of British Columbia, Vancouver, British Columbia, Canada; Vancouver Coastal Health Authority, Vancouver, British Columbia, Canada (C.B.F., G.W.); Fraser Health Authority, Vancouver, British Columbia, Canada (M.P.); School of Nursing, University of British Columbia, Vancouver, British Columbia, Canada (M.M.); St. Paul's Hospital Heart Centre, Vancouver, British Columbia, Canada (M.M.); School of Population and Public Health (J.S.) and Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada (R.D.T.).

Sources of Funding

This study was funded by the Vancouver Coastal Health Research Institute.

Disclosures

Dr Cairns has received research grant support from Medtronic, Sanofi Aventis, AstraZeneca, Bayer, Boston Scientific, and Edwards Laboratories; has received speaker honoraria from Pfizer/BMS, Bayer, and Servier; has received consulting fees from St Jude Medical, Bayer, BMS, and Servier; DSMBs: ARTESiA (apixaban; CIHR, BMS), COMPASS (rivaroxaban; Bayer); and ATLASiCD (CIHR, Boston Scientific), OCEAN (rivaroxaban; CIHR, Bayer, Biotronik). Dr Fordyce serves on advisory boards for Bayer, Novo Nordisk, Boehringer Ingelheim, and Sanofi. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1–S2

REFERENCES

- Rao KK, Enriquez JR, De Lemos JA, Alexander KP, Chen AY, McGuire DK, Fonarow GC, Das SR. Use of aldosterone antagonists at discharge after myocardial infarction: results from the National Cardiovascular Data Registry Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get with the Guidelines (GWTG). *Am Heart J*. 2013;166:709–715. DOI: 10.1016/j.ahj.2013.06.020.
- Sutton NR, Li S, Thomas L, Wang TY, de Lemos JA, Enriquez JR, Shah RU, Fonarow GC. The association of left ventricular ejection fraction with clinical outcomes after myocardial infarction: findings from the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry-Get With the Guidelines (GWTG) Medicare-linked database. *Am Heart J*. 2016;178:65–73. DOI: 10.1016/j.ahj.2016.05.003.
- Miller AL, Dib C, Li L, Chen AY, Amsterdam E, Funk M, Saucedo JF, Wang TY. Left ventricular ejection fraction assessment among patients with acute myocardial infarction and its association with hospital quality of care and evidence-based therapy use. *Circ Cardiovasc Qual Outcomes*. 2012;6:662–671. DOI: 10.1161/CIRCOUTCOMES.112.965012.
- O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, 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. *Circulation*. 2013;127:529–555. DOI: 10.1161/CIR.0b013e3182742c84.
- Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *Circulation*. 2004;110:588–636. DOI: 10.1161/01.CIR.0000134791.68010.FA.
- Jeger R, Ben LH, Sujayeva V, Dizdarevic-Hudic L, Kastrati A, Terkelsen PJ, Bertelli L, Simpson IA, Gilard M, Karamfiloff K, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2017;39:119–177. DOI: 10.1093/eurheartj/ehx393.
- Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321. DOI: 10.1056/NEJMoA030207.
- Pitt B, White H, Nicolau J, Martinez F, Gheorghiadu M, Aschermann M, van Veldhuisen DJ, Zannad F, Krum H, Mukherjee R, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardiol*. 2005;46:425–431. DOI: 10.1016/j.jacc.2005.04.038.
- Adamopoulos C, Ahmed A, Fay R, Angioi M, Filippatos G, Vincent J, Pitt B, Zannad F; EPHEsus Investigators. Timing of eplerenone initiation and outcomes in patients with heart failure after acute myocardial infarction complicated by left ventricular systolic dysfunction: insights from the EPHEsus trial. *Eur J Heart Fail*. 2009;11:1099–1105. DOI: 10.1093/eurjhf/hfp136.
- Hayashi M, Tsutamoto T, Wada A, Tsutsui T, Ishii C, Ohno K, Fujii M, Taniguchi A, Hamatani T, Nozato Y, et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodeling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation*. 2003;107:2559–2565. DOI: 10.1161/01.CIR.0000068340.96506.0F.
- Brandimarte F, Blair JEA, Manuchehry A, Fedele F, Gheorghiadu M. Aldosterone receptor blockade in patients with left ventricular systolic dysfunction following acute myocardial infarction. *Cardiol Clin*. 2008;26:91–105. DOI: 10.1016/j.ccl.2007.08.011.
- Rassi AN, Cavender MA, Fonarow GC, Cannon CP, Hernandez AF, Peterson ED, Peacock WF, Laskey WK, Rosas SE, Zhao X, et al. Temporal trends and predictors in the use of aldosterone antagonists post-acute myocardial infarction. *J Am Coll Cardiol*. 2013;61:35–40. DOI: 10.1016/j.jacc.2012.08.1019.
- López-de-Sá E, Martínez A, Anguita M, Dobarro D, Jiménez-Navarro M. Aldosterone receptor antagonist use after myocardial infarction. data from the REICIAM registry. Article in Spanish. *Rev Esp Cardiol*. 2011;64:981–987. DOI: 10.1016/j.recesp.2011.06.013.
- Fordyce CB, Cairns JA, Singer J, Lee T, Park JE, Vandegriend RA, Perry M, Largy W, Gao M, Ramanathan K, et al. Evolution and impact of a regional reperfusion system for ST-elevation myocardial infarction. *Can J Cardiol*. 2016;32:1222–1230. DOI: 10.1016/j.cjca.2015.11.026.
- Moghaddam N, Wong GC, Cairns JA, Goodman SG, Perry-Arnesen M, Tocher W, Mackay M, Singer J, Lee T, Rao SV, et al. Association of anemia with outcomes among ST-segment-elevation myocardial infarction patients receiving primary percutaneous coronary intervention. *Circ Cardiovasc Interv*. 2018;11:e007175. DOI: 10.1161/CIRCINTERVENTIONS.118.007175.
- Ambrosy AP, Pang PS, Khan S, Konstam MA, Fonarow GC, Traver B, Maggioni AP, Cook T, Swedberg K, Burnett JC, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J*. 2013;34:835–843. DOI: 10.1093/eurheartj/ehs444.
- Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018;72:351–366. DOI: 10.1016/j.jacc.2018.04.070.
- Savarese G, Carrero J-J, Pitt B, Anker SD, Rosano GMC, Dahlström U, Lund LH. Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2018;20:1326–1334. DOI: 10.1002/ejhf.1182.
- Ferreira JP, Rossello X, Pitt B, Rossignol P, Zannad F. Eplerenone in patients with myocardial infarction and “mid-range” ejection fraction: an analysis from the EPHEsus trial. *Clin Cardiol*. 2019;42:1106–1112. DOI: 10.1002/clc.23261.
- Serenelli M, Jackson A, Dewan P, Jhund PS, Petrie MC, Rossignol P, Campo G, Pitt B, Zannad F, Ferreira JP, et al. Mineralocorticoid receptor antagonists, blood pressure, and outcomes in heart failure with reduced ejection fraction. *JACC Heart Fail*. 2020;8:188–198. DOI: 10.1016/j.jchf.2019.09.011.
- Dyrkorn R, Langaas HC, Giverhaug T, Espnes KA, Rowett D, Spigset O. Academic detailing as a method of continuing medical education. *Adv Med Educ Pract*. 2019;10:717–725. DOI: 10.2147/AMEP.S206073.

-
22. Agee N, Komenaka IK, Drachman D, Bouton ME, Caruso DM, Foster KN. The effectiveness of grand rounds lectures in a community-based teaching hospital. *J Surg Educ.* 2009;66:361–366. DOI: 10.1016/j.jsurg.2009.07.006.
 23. Tsuyuki RT, Al Hamarneh YN, Jones CA, Hemmelgarn BR. The effectiveness of pharmacist interventions on cardiovascular risk. *J Am Coll Cardiol.* 2016;67:2846–2854. DOI: 10.1016/j.jacc.2016.03.528.
 24. Bhat S, Kansal M, Kondos GT, Groo V. Outcomes of a pharmacist-managed heart failure medication titration assistance clinic. *Ann Pharmacother.* 2018;52:724–732. DOI: 10.1177/1060028018760568.
 25. Kao DP, Trinkley KE, Lin C-T. Heart failure management innovation enabled by electronic health records. *JACC Heart Fail.* 2020;8:223–233. DOI: 10.1016/j.jchf.2019.09.008.

SUPPLEMENTAL MATERIAL

Table S1. Association between expanded list of variables and MRA prescription at discharge among MRA-eligible STEMI patients.

	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	P value
LVEF (per 5% decrease)	1.53 (1.26-1.87)	1.52 (1.23-1.88)	<0.001
Calendar year (per year increase)	1.22 (1.10-1.35)	1.24 (1.12-1.38)	<0.001
Age, per 10-year decrease	1.14 (0.93-1.40)	1.09 (0.85-1.38)	0.500
Male	1.23 (0.63-2.39)	1.37 (0.63-2.96)	0.422
Non-anterior location	0.99 (0.52-1.88)	1.17 (0.58-2.38)	0.656
Non-PCI capable hospital	1.36 (0.78-2.37)	1.39 (0.76-2.53)	0.287
Hospital length-of-stay, per day increase	1.00 (0.98-1.02)	1.00 (0.98-1.02)	0.940
No ACEI/ARB use within 24 hours of presentation	1.58 (0.84-2.99)	1.35 (0.64-2.86)	0.437
Diabetes mellitus	0.50 (0.29-0.86)	0.54 (0.29-1.00)	0.051
Peak creatinine, per 10 µmol/L decrease	1.02 (0.97-1.07)	1.05 (0.98-1.12)	0.182

*Multivariable adjustment for other covariates listed in this table.

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CI: Confidence interval; LVEF: Left ventricular ejection fraction, OR: odds ratio, PCI: Percutaneous coronary intervention.

Table S2. Association between expanded list of variables and MRA prescription at discharge among MRA-eligible STEMI patients with history of diabetes (n=151).

	Adjusted* OR (95% CI)	P value
LVEF (per 5% decrease)	1.43 (1.01-2.02)	0.046
Calendar year (per year increase)	1.30 (1.09-1.56)	0.004
Age, per 10-year decrease	1.13 (0.74-1.73)	0.560
Male	1.60 (0.44-5.90)	0.478
Non-anterior location	1.76 (0.64-4.88)	0.276
Non-PCI capable hospital	1.86 (0.72-4.82)	0.199
Hospital length-of-stay, per day increase	1.02 (0.96-1.07)	0.565
No ACEI/ARB use within 24 hours of presentation	0.56 (0.07-4.55)	0.590
Peak creatinine, per 10 µmol/L decrease	1.03 (0.93-1.14)	0.548

*Multivariable adjustment for other covariates listed in this table.

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CI: Confidence interval; LVEF: Left ventricular ejection fraction, OR: odds ratio, PCI: Percutaneous coronary intervention.