





ORIGINAL RESEARCH

# Characteristics and Outcomes of Early Recurrent Myocardial Infarction After Acute Myocardial Infarction

Raunak Nair, MD; Michael Johnson, MD; Kathleen Kravitz, MBA, RN; Chetan Huded, MD, Msc; Jeevanantham Rajeswaran, PhD; Moses Anabila, MS; Eugene Blackstone , MD; Venu Menon , MD; A. Michael Lincoff, MD; Samir Kapadia , MD; Umesh N. Khot , MD

**BACKGROUND:** We aimed to understand the characteristics and outcomes of patients readmitted with a recurrent myocardial infarction (RMI) within 90 days of discharge after an acute myocardial infarction (early RMI).

**METHODS AND RESULTS:** We analyzed the timing of reinfarction, etiology, and outcome for all patients admitted with an early RMI within 90 days of discharge after an acute myocardial infarction between January 1, 2010 and January 1, 2017. We identified 6626 admissions for acute myocardial infarction (index myocardial infarction) which led to 168 cases of RMI within 90 days of discharge. The mean patient age was 65.1±13.1 years, and 37% were women. The 90-day probability of readmission with an early RMI was 2.5%. Black race, medical management, higher troponin T, and shorter length of stay were independent predictors of early RMI. Medically managed group had a higher risk for early RMI compared with percutaneous coronary intervention ( $P=0.04$ ) or coronary artery bypass grafting ( $P=0.2$ ). Predominant mechanisms for reinfarction were stent thrombosis (17%), disease progression (12%), and unchanged coronary artery disease (11%). At 5 years, the all-cause mortality rate for patients with an early RMI was 49% (95% CI, 40%–57%) compared with 22% (95% CI, 21%–23%) for patients without an early RMI ( $P<0.0001$ ).

**CONCLUSIONS:** Early RMI is a life-threatening condition with nearly 50% mortality within 5 years. Stent-related events and progression in coronary artery disease account for most early RMI. Medication compliance, aggressive risk factor management, and care transitions should be the cornerstone in preventing early RMI.

**Key Words:** coronary artery disease ■ early recurrent myocardial infarction ■ readmission ■ reinfarction ■ stent thrombosis

In the United States, every 40 seconds a person develops an acute myocardial infarction (AMI), contributing to an annual healthcare expenditure of around \$351 billion.<sup>1</sup> Because of the considerable morbidity and mortality associated with an AMI, over the last decade, there has been a significant emphasis on enhancing procedural techniques, developing newer stents, and strengthening secondary prevention, all of which have transformed the care of patients with myocardial infarction (MI). Although these interventions have led to a decrease in the overall mortality rate,<sup>2</sup>

survivors of an MI remain at increased risk for further adverse cardiovascular events.<sup>3–5</sup> One of the most concerning of these adverse events is a recurrent myocardial infarction (RMI).

Around 10% of all MI patients are at risk of developing an RMI within the next year.<sup>5</sup> Studies have also shown that around 200 000 recurrent myocardial infarctions are estimated to occur in the United States annually.<sup>1</sup> Such re-infarctions can have a tremendous physical, emotional, and economic impact on the patients and society.<sup>6</sup> In addition, they lead to

Correspondence to: Umesh N. Khot, MD, Heart, Vascular and Thoracic Institute Center for Healthcare Delivery Innovation, Cleveland Clinic, 9500 Euclid Avenue/J2-4, Cleveland, OH 44195. E-mail: khotu@ccf.org

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## CLINICAL PERSPECTIVE

### What Is New?

- Most early recurrent myocardial infarctions will occur within 2 weeks of discharge after an acute myocardial infarction.
- Stent-related events and progression in coronary artery disease account for most early recurrent myocardial infarction.
- Approximately 50% of patients with an early recurrent myocardial infarction die within 5 years.

### What Are the Clinical Implications?

- Factors contributing to recurrent infarctions are at play even before patients are discharged, so effective planning of care transitions is important.
- Emphasis on medication adherence and aggressive risk factor management should continue to be the cornerstone in treating patients with myocardial infarction.
- Since patients without intervention had worse outcomes, thorough evaluation for intervention opportunities may need to be adopted in the management of patients with early recurrent myocardial infarction.

## Nonstandard Abbreviations and Acronyms

<b>LHC</b>	left heart catheterization
<b>RMI</b>	recurrent myocardial infarction

unplanned readmissions which worsen the burden on healthcare economy.<sup>7</sup> RMI occurring after 90 days has been associated with significantly worse outcomes in patients with ST-segment-elevation myocardial infarction (STEMI) treated with percutaneous coronary intervention (PCI).<sup>8–10</sup> Furthermore, in patients with left ventricular dysfunction or heart failure post-MI, RMI has been associated with a 1-year mortality of about 38%.<sup>11</sup> With the burden of coronary artery disease expected to increase almost 7-fold in the future,<sup>12</sup> the absolute incidence of RMI is expected to rise substantially. Although the incidence, prognosis, and risk factors associated with developing a late RMI have been described before, little is known about the pattern and characteristics of patients who develop an early recurrent MI during the initial 90-day period after an acute MI. Our study aims to understand these characteristics and define the outcomes for all patients who develop an early RMI within 90 days of discharge after an AMI.

## METHODS

Because of the patient specific nature of our data, we will not be able to share it with individuals outside of this research project. Our study was done at the Cleveland Clinic main campus. The Cleveland Clinic health system consists of 11 hospitals, which include a main campus academic medical center and 10 regional hospitals across Northeast Ohio. We retrospectively identified all patients who were admitted to our main campus with a principal diagnosis of MI from January 1, 2010 to January 1, 2017, using discharge *International Classification of Diseases, Ninth Revision (ICD-9)*, diagnosis codes, including both STEMI and non-ST-segment-elevation MI (NSTEMI) (*ICD-9* codes 410–410.9). Patients who died during their index admission for MI were excluded, and only patients discharged alive after MI remained in the study cohort. All readmissions planned and unplanned, for any reason to any hospital within our institutional health system (including the main campus hospital and all regional hospitals in Northeast Ohio) within 90 days of the index MI were identified using our institutional billing system. If a patient was readmitted after 90 days of index admission, that readmission was considered as a new index admission for MI. Readmissions to hospitals outside of our health system were not available and not included in the analysis. After a readmission was identified, patients remained in the study cohort because they continued to be at risk for readmission.

Baseline demographic data during the index admission and readmission were collected for all patients. Readmission within 90 days, for a recurrent myocardial infarction, admitted to any of the Cleveland Clinic Health System hospital remained our primary end point of interest. These were identified using the institutional billing system. The date of discharge was considered as time zero. Patients with index MI were categorized according to treatment strategy into medical management, PCI, and coronary artery bypass grafting. Physician directed chart review was done on all patients with RMI to understand etiology behind reinfarction. The etiologies were further categorized into (1) stent thrombosis, (2) in-stent restenosis, (3) disease progression which indicates progression in atherosclerosis in an artery with known coronary artery disease from index MI, (4) unchanged coronary artery disease defined when left heart catheterization (LHC) during RMI showed similar findings as the LHC during index MI, (5) new vessel disease which was defined as new obstruction or stenosis in a vessel that had normal flow in the LHC performed during index MI. This also includes all patients who did not have prior LHC and patients who developed a graft occlusion following a CABG done during index MI, and (6) planned procedure which includes all patients who were readmitted

for a planned intervention. Patients with new vessel disease were further classified as new vessel obstruction or non-obstructive coronary artery disease depending on how the lesion was categorized during the angiogram. The study protocol was approved by our Institutional Review Board, with a waiver of informed consent.

Simple descriptive statistics used to summarize the data. Continuous variables are presented as mean±SD or as median [interquartile range] when the variable is skewed and were compared using Wilcoxon rank-sum test. Categorical data are described using frequencies and percentages and were compared using the Chi-squared test. All analyses were performed using SAS statistical software (SAS v9.4; SAS, Inc., Cary, NC). Because patients can be readmitted more than once during follow-up, and each readmission is of varying duration, we used analytic methods for repeated, time-related events rather than traditional time-to-first-event (survival) analysis. Therefore, unlike survival-type analysis, patients remain at risk for another event after experiencing an event. Instantaneous risk (hazard function) of repeated readmissions was estimated by the multi-phase parametric method.<sup>13</sup>

Time varying hazard of readmission for MI analysis yielded an early peaking phase followed by a late slightly increasing phase. In the multivariable analysis, factors modulating both hazard phases are considered simultaneously using the multi-phase parametric model. All the variables listed in Data S1, are considered during variable selection in both phases, simultaneously. Variable selection used a computer-intensive machine learning “bagging” method (bootstrap aggregation).<sup>14</sup>

Survival analysis was performed using Kaplan–Meier non-parametric method and simple comparisons were made using the log-rank test. The date of death was ascertained by manual search in the electronic medical records and in certain cases from online obituaries. An exact match was required between the obituary and the electronic medical records in at least 3 of the following 4 characteristics: first and last name, age or date of birth, place of residence, and next of kin. Median follow-up for mortality was 4 years and a total of 22 106 patient-years were available for analysis; 10% of the survivors were followed for >8 years.

## RESULTS

We were able to identify 6626 admissions for acute MI (by 6328 patients) at our hospital from January 1, 2010, to January 1, 2017. These lead to a total of 2051 readmissions within 90 days (by 1389 patients), out of which 168 readmissions were for an early RMI (from 155 index admission cases). (Figure 1).

## Baseline Characteristics

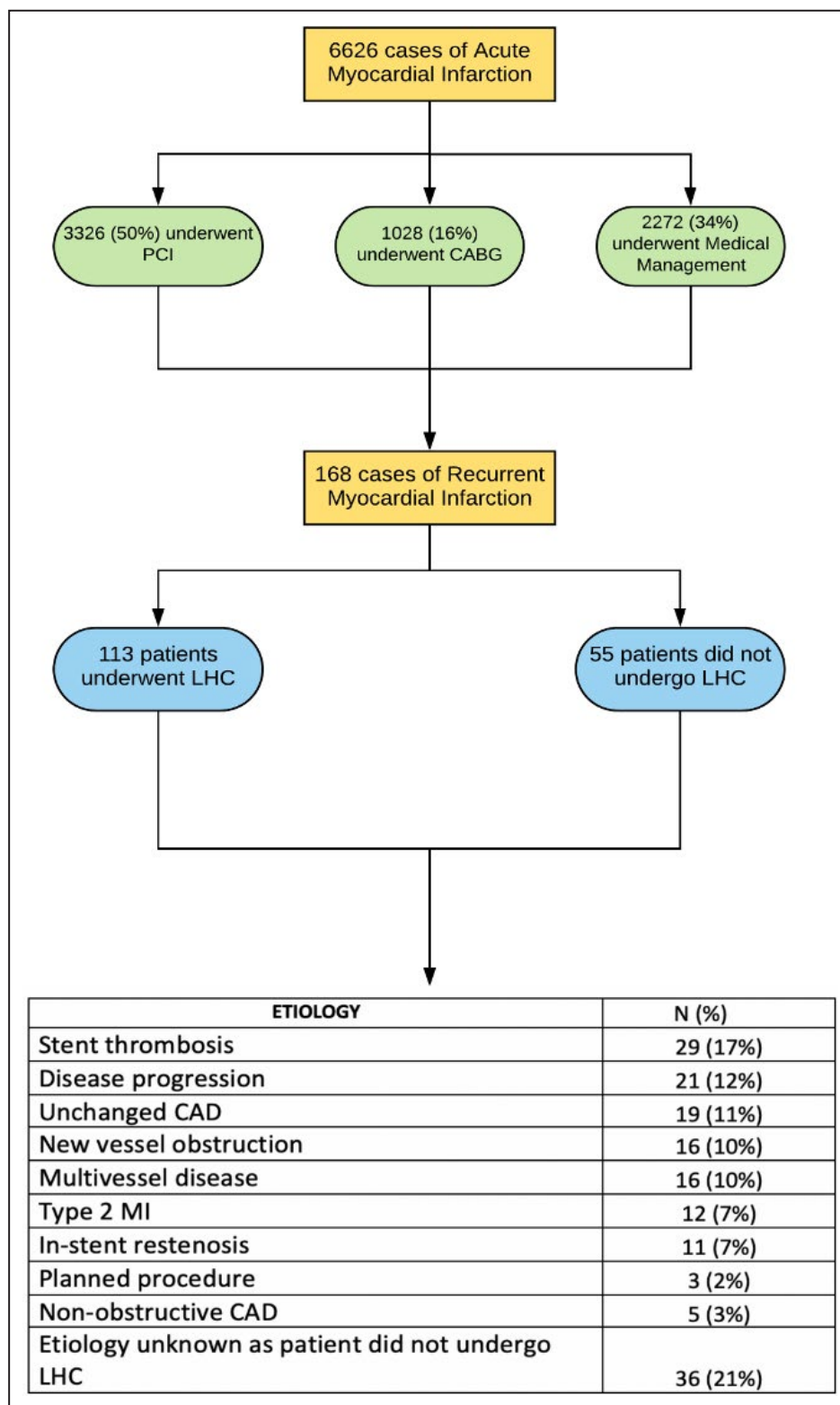
For the 6471 index MI cases (these are the index MI cases who did not get an early RMI obtained by removing the 155 cases from the total 6626 cases of index MI), the mean age was 65.1±13.1 years, 37% were women, and 25% were Black. Mean peak troponin T, left ventricular ejection fraction, and length of stay was 2.25±3.65, 47.1±13.5, and 7.5±8.7. Compared with them, the mean age for patients who developed recurrent MI was 65 years, 39% were women, and 37% were Black patients. The mean peak troponin T, left ventricular ejection fraction, and length of stay for RMI cases were 2.29±4.34, 46.5±13.4, and 6.41±7.24. Baseline characteristics are presented in Table 1.

Compared with the index MI cases without RMI, patients admitted with an early RMI had a higher prevalence of smoking, diabetes mellitus, dyslipidemia, chronic kidney disease, congestive heart failure, and dialysis. The prevalence of coronary artery disease was similar between patients with index MI and RMI. Though NSTEMI was the predominant subtype in both groups, patients with early RMI had a higher proportion of NSTEMI when compared with patients with index MI, (78% versus 71%).

## Timing and Index Hospitalization Factors Affecting RMI

There was a total of 168 readmissions for early recurrent MI amongst 155 index admission for MI cases; 142 index cases were readmitted once and 13 cases were readmitted twice within 90 days. The instantaneous risk of readmission with an early recurrent MI peaked at 2 days after hospital discharge and the vast majority occurred within the first 2 weeks after hospital discharge (Figure 2A). The risk of readmission for early RMI stratified by index MI treatment strategy into PCI, CABG, and medical management revealed that the CABG group appeared to have the lowest risk of readmission with an early RMI and that there was no significant difference in the late risk (30–90 day) of readmission between PCI and CABG groups ( $P=0.8$ ). Overall, the medically managed group had the highest risk of readmission with an early RMI (Figure 2B).

Multivariable analysis also showed that certain characteristics such as belonging to Black race ( $P=0.05$ ), a higher peak troponin T ( $P=0.002$ ), shorter length of index hospitalization ( $P<0.0001$ ), lower hemoglobin during admission ( $P=0.04$ ), and being medically managed ( $P=0.0006$ ) were independently associated with a higher risk of readmission with an early RMI (Table 2). Risk factor analysis for time to first RMI yielded similar results (Table S1).



**Figure 1. Causes of early recurrent myocardial infarction after acute myocardial infarction.**

Out of 55 patients who did not undergo catheterization, 12 had type 2 myocardial infarction, 7 had known multivessel disease and hence underwent coronary artery bypass grafting and the reason for recurrent myocardial infarction for the remaining 36 is unknown. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; LHC, left heart catheterization; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

**Table 1. Baseline Characteristics From Index Hospitalization for Patients With and Without Early Recurrent MI**

Label	Patients Without Early RMI (N=6471)		Patients With Early RMI (N=155)		P Value
	# (% of n)	n (% of N)	# (% of n)	n (% of N)	
Characteristics at admission					
Demographics					
Calculated age, y	6471	65.1±13.1	155	64.9±12.6	0.7
Body mass index	6171	29.3±6.63	147	28.7±6.91	0.13
Patient sex: female	2366 (37)	6466 (100)	61 (39)	155 (100)	0.5
Race: White	4645 (72)	6471 (100)	93 (60)	155 (100)	0.001
Race: Black	1579 (24)	6471 (100)	58 (37)	155 (100)	0.0002
Race: Other than Black and White*	247 (3.8)	6471 (100)	4 (2.6)	155 (100)	0.4
Non-cardiac comorbidities					
Smoking history	3973 (61)	6471 (100)	105 (68)	155 (100)	0.11
Diabetes mellitus	2941 (45)	6471 (100)	80 (52)	155 (100)	0.13
Dyslipidemia	5234 (81)	6471 (100)	131 (85)	155 (100)	0.2
Chronic kidney disease	1551 (24)	6471 (100)	50 (32)	155 (100)	0.02
Dialysis	339 (5.2)	6471 (100)	12 (7.7)	155 (100)	0.17
Cardiac comorbidities					
History of CAD	5938 (92)	6471 (100)	142 (92)	155 (100)	>0.9
Hypertension	5572 (86)	6471 (100)	133 (86)	155 (100)	>0.9
History of CHF	1796 (28)	6471 (100)	51 (33)	155 (100)	0.16
MI subtype					
STEMI	1900 (29)	6471 (100)	34 (22)	155 (100)	0.04
Non-STEMI	4571 (71)	6471 (100)	121 (78)	155 (100)	0.04
Laboratory values on admission					
Peak BNP during admission	1714	183[493]	30	137 [494]	0.15
Lowest hemoglobin during admission	6399	10.9±2.53	154	10.7±2.36	0.6
Peak creatinine during admission	6402	1.7±1.74	155	1.94±2.06	0.15
Peak troponinT during admission	6343	0.86 [2.32]	152	0.86 [1.48]	>0.9
Peak CKMB during admission	6234	16 [60]	149	18 [44]	0.8
Peak CK during admission	6284	306 [749]	153	279 [547]	0.4
Left ventricular function					
LVEF on presentation	5836	47.1±13.5	132	46.5±13.4	0.6
LHC					
LHC (Diagnostic catheterization) performed	4997 (77)	6471 (100)	115 (74)	155 (100)	0.4
Door-to-balloon in min (STEMI)	1202	102±75.9	24	107±64.5	0.8
Procedure					
PCI	3255 (50)	6471 (100)	71 (46)	155 (100)	0.3
CABG	1016 (16)	6471 (100)	12 (7.7)	155 (100)	0.007
Medically managed	2200 (34)	6471 (100)	72 (46)	155 (100)	0.001
Characteristics at discharge					
Laboratory values at discharge					
Discharge hemoglobin	6399	11.7±2.3	154	11.5±2.12	0.4
Discharge creatinine	6402	1.35±1.26	144	1.6±1.65	0.15
Medications at discharge					
ACE inhibitors	3307 (52)	6360 (98)	86 (55)	155 (100)	0.4
Beta blockers	5756 (91)	6360 (98)	142 (92)	155 (100)	0.6
P2Y12 inhibitors	4378 (69)	6360 (98)	111 (72)	155 (100)	0.5
Anticoagulants	853 (13)	6360 (98)	20 (13)	155 (100)	0.8

(Continued)

**Table 1. Continued**

Label	Patients Without Early RMI (N=6471)		Patients With Early RMI (N=155)		P Value
	# (% of n)	n (% of N)	# (% of n)	n (% of N)	
Aldosterone antagonists	390 (6.1)	6360 (98)	8 (5.2)	155 (100)	0.6
ARB	626 (9.8)	6360 (98)	10 (6.5)	155 (100)	0.16
Aspirin	6133 (96)	6360 (98)	146 (94)	155 (100)	0.14
Statins	5918 (93)	6360 (98)	149 (96)	155 (100)	0.13
Length of stay					
Hospital Length of stay (days)	6471	4 [7]	155	4 [6]	0.04

ACE indicates angiotensin-converting enzymes; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CK, creatine kinase; CKMB, creatine kinase myocardial band; LHC, left heart catheterization; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

\*Other races include all races other than African-American and Caucasians and primarily included Asians and Hispanics\*.

## Etiology and Management

Around 67% of patients with RMI had a diagnostic LHC. The etiologies of early RMI are summarized in Figure 1. The most common reasons for readmission with a RMI were found to be stent thrombosis (17%) and disease progression (12%) (Figure 1). Around 10% of patients had developed new vessel involvement and 7% were readmitted because of in-stent restenosis; 7% of all recurrent MI patients were found to have type 2 MI. Amongst the 37% of patients who did not undergo LHC, 13% had contraindications to the procedure and 6% of patients declined to have a procedure.

About 46% of patients with RMI underwent PCI, 8% underwent CABG, and 46% of patients with RMI were decided to continue with medical management (Table 1).

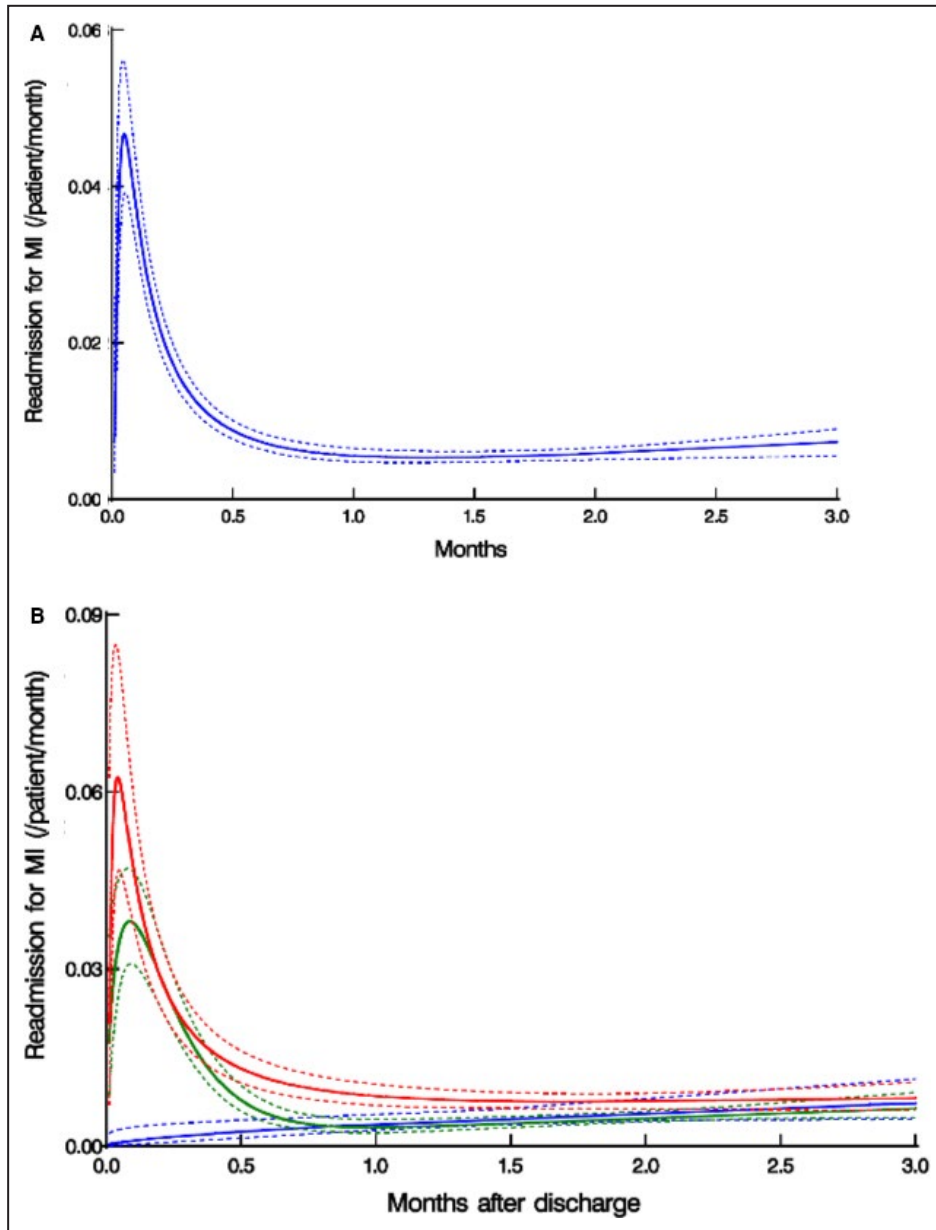
## Mortality

Out of 168 cases for early recurrent MI, there were 78 deaths. As illustrated in Figure 3A, the unadjusted all-cause mortality was 30% (95% CI, 23%–38%) at 1 year and continued to rise steadily beyond the first year. Mortality was 44% (95% CI, 36%–52%) at 3 years and 49% (95% CI, 40%–57%) at 5 years. The probability of mortality stratified by MI subtypes in patients with RMI revealed that patients readmitted with STEMI did significantly better than patients who were readmitted with NSTEMI ( $P=0.008$ ) (Figure 3B). Mortality for patients who did not develop an early RMI was lower, with the unadjusted all-cause mortality for 30 days, 1, 3, and 5 years being 0.60% (95% CI, 0.40%–0.80%), 5.4% (95% CI, 4.7%–6.0%), 13% (95% CI, 12%–14%), and 22% (95% CI, 21%–23%) (Figure 3A). Mortality rates were also lower for patients with early RMI who developed stent thrombosis compared with patients with RMI who did not have stent thrombosis (5-year survival, 76% versus 47%,  $P=0.06$ , Figure S1).

## DISCUSSION

Our study reveals several key findings pertaining to the disease course and the management of patients with early RMI. Notably, we show that patients who are admitted with an AMI are at the highest risk of developing an early RMI during the first 2 days after discharge and that this risk remains elevated during the initial 2 weeks postdischarge. We also saw that patients who were medically managed had a higher chance of developing reinfarction within 90 days than patients who were revascularized. Multivariate analysis revealed that Black race, medical management, higher troponin T, and shorter length of stay were independent predictors of an early RMI. Though several mechanisms were contributing to the development of an early RMI, we found that a stent-related event was the most common. Also, patients with early RMI who were admitted with STEMI had a significantly better prognosis than patients who were readmitted with an NSTEMI. Overall, patients with an early RMI had a worse prognosis than patients without an early RMI, with only half of the patients surviving at 5 years.

The temporal pattern of reinfarctions after an index MI remains unclear. In our study, we demonstrate that for patients with AMI, the initial 2 weeks after discharge is a “high-risk” period. Furthermore, we were able to narrow the timeframe and reveal that the first 2 days after discharge is the most crucial to these patients. This signifies that factors that promote reinfarction are probably in play even before patients leave the hospital. Focusing on transitions of care is pivotal to improve the outcomes for these patients. Predischage planning, patient education with readback, incorporating health information technology, proper medication reconciliation, scheduling appropriate follow-up appointments before discharge, follow-up telephone calls, and postdischarge home visits are all effective methods that should be implemented to reduce the pitfalls



**Figure 2.** Timing of early recurrent myocardial infarction (RMI) and relationship with index myocardial infarction treatment strategies.

**A,** Timing of readmission with early RMI. Instantaneous risk (hazard function, or rate) of readmission for early RMI (RMI, solid line) enclosed within dashed 68% confidence bands. Note that early peaking hazard followed by a slightly increasing risk (almost constant risk at a rate of about 0.01 readmissions for myocardial infarction per patient per month). **B,** Relationship between index myocardial infarction treatment strategy and risk of early RMI. Instantaneous risk (or rate) of readmissions for early RMI hazard after admission for acute myocardial infarction stratified by treatment strategy. Solid line is the parametric estimates of the instantaneous risk of readmission for myocardial infarction enclosed within a 68% CI. MI indicates myocardial infarction.

surrounding the transition of care.<sup>15–18</sup> In most cases, the incorporation of multiple interventions at the same time is more successful in preventing readmissions as compared with solitary interventions.<sup>19–21</sup> Stent thrombosis and in-stent restenosis accounted for around one fourth of all early RMI

events. Also, 12% of patients developed disease progression of a previously stenosed vessel and 10% of patients developed stenosis of a new vessel that led to an early RMI. Patients who develop an AMI have been proposed to have a persistent proinflammatory state following the acute episode that

**Table 2. Incremental Risk Factors for Early RMI During Days 0 to 30 and 31 to 90**

Risk Factor	Coefficient±SE	HR (95% CI)*	P Value	R <sup>†</sup> (%)
Early hazard phase				
Race: Black	0.65±0.23	1.9 (1.2–3.0)	0.005	50
Higher peak troponinT <sup>‡</sup>	0.26±0.086		0.002	77
Treatment: medically managed	0.84±0.24	2.3 (1.4–3.7)	0.0006	60
Shorter index length of stay <sup>§</sup>	0.43±0.11		<0.0001	94
Late hazard phase				
Lower HGB during admission <sup>  </sup>	−0.53±0.26		0.04	51

Because there are 2 distinct phases of risk with different drivers during each period, we stratified the cases of early recurrent myocardial infarction into early (0–30 days) and late phase (30–90 days). RMI indicates recurrent myocardial infarction.

\*Hazard ratio was not estimated for continuous variables with non-linear transformation.

<sup>†</sup>Bagging reliability— interpreted as the probability of  $P < 0.05$  and represents the proportion of 1000 bootstrap analyses in which this variable was retained with  $P < 0.05$ .

<sup>‡</sup>Log [peak troponinT during admission], logarithmic transformation.

<sup>§</sup>[Index admission length of stay], inverse transformation.

<sup>||</sup>[Lowest hemoglobin (HGB) during admission]<sup>2</sup>, squared transformation.

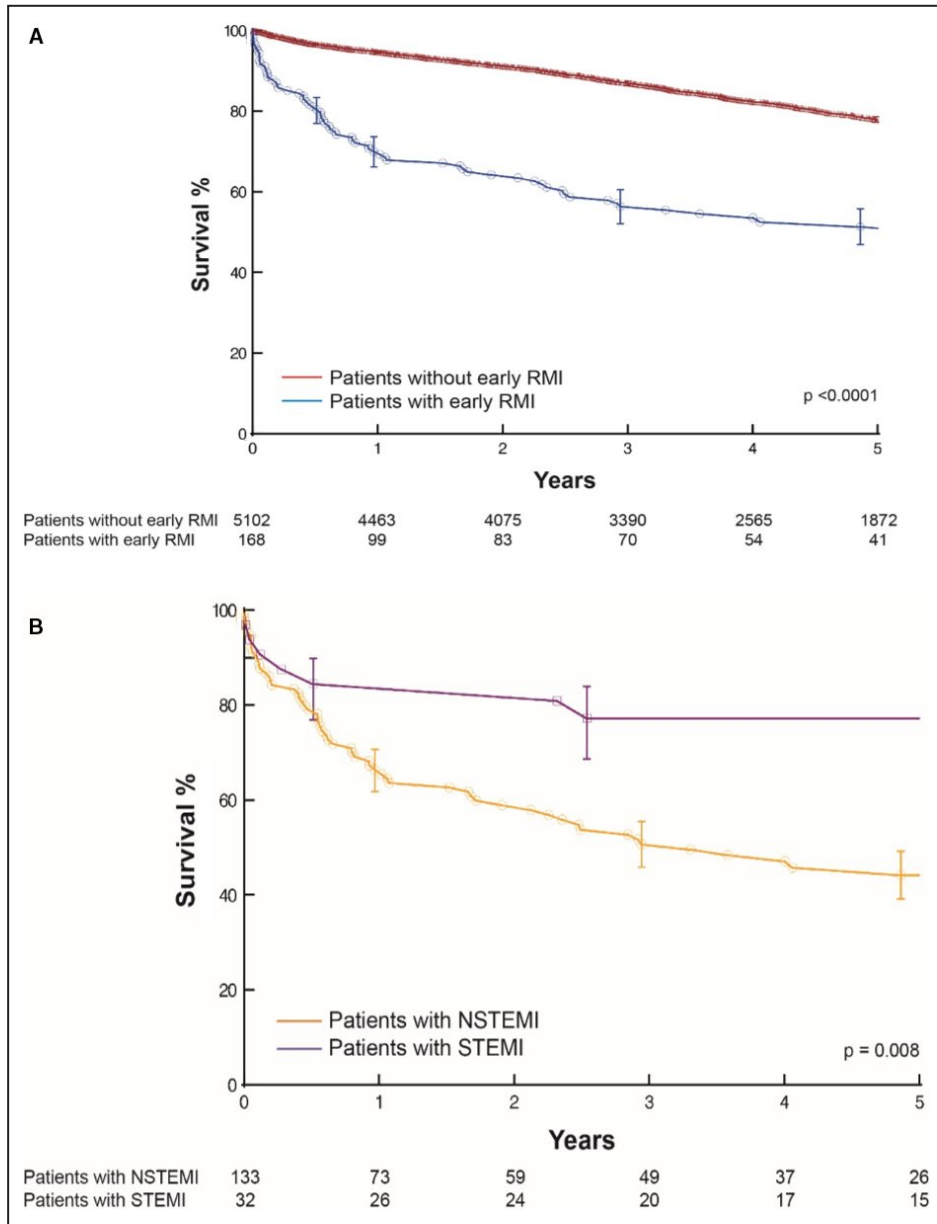
predisposes them to further adverse events.<sup>22–26</sup> The rapid progression of coronary artery disease and the development of new obstructive diseases could be the result of such an extended inflammatory response. The success of medications with anti-inflammatory effects such as aspirin, statin, and canakinumab in reducing recurrent cardiovascular events after MI supports this theory.<sup>27–29</sup> Thus, ensuring that patients are on guideline-directed medical therapy and emphasizing on the importance of medication adherence are the most vital steps to prevent such reinfarctions. Studies have shown that a significant number of patients delay filling their prescriptions after discharge which increases the risk of adverse events.<sup>30,31</sup> Hospitals can adopt bedside medication delivery to ensure that patients have the appropriate medications refilled at least for the next 30 days to prevent them from missing these essential drugs. Telemedicine visits can also be incorporated to check in on patient status and to address any questions postdischarge.

In our study, we were also able to identify few independent variables that were associated with a higher risk of developing an early RMI such as belonging to the Black race, higher peak troponin T, shorter length of hospitalization, and lower hemoglobin during admission. These characteristics are in line with previous studies that have shown race, renal dysfunction, and higher troponin levels to be predictors of poor prognosis after MI.<sup>32–34</sup> Also, we have shown that patients who did not undergo an intervention during the index MI have a higher chance of developing an early RMI. Defining such characteristics can help to form a “reinfarction risk model”, which can identify patients at a higher risk of reinfarction than others. Forming such a profile of high-risk patients can be beneficial in targeting interventions and resources towards the most

vulnerable group of patients. With payment systems moving towards a value for quality rather than quantity, such risk models can also assist hospitals to reduce the burden of penalizations imposed under the Hospital Readmission Reduction Program.<sup>35,36</sup> Though the incidence of RMI has been progressively declining over the years with the application of high-value care and advancements in medicine, the mortality rate of these subsets of patients remains high. At 1 year, the all-cause mortality rate of patients with early RMI in our cohort was significantly higher than that of patients who did not develop an early RMI. A cumulative effect of the recurrent myocardial damage, prolonged inflammation, reperfusion injuries, and left ventricular remodeling might have a role to play in this.<sup>37–41</sup> We also noted that patients with RMI with an STEMI did better when compared with patients with RMI with an NSTEMI. We believe that the timely intervention in all of our patients with STEMI may be an important contributor towards their better prognosis. Mortality rates were also higher for patients with early RMI who did not undergo an intervention; This might imply that an aggressive strategy might need to be adopted when managing these patients. However, since the majority of patients who did not undergo an intervention had contraindications or were opted for medical management, these were already patients who had a poor prognosis. Further studies are needed to assess if the adoption of an aggressive management model translates to improved outcomes in these patients.

Our study has certain limitations. Since our study was limited to hospitals within our enterprise, readmissions to hospitals outside our health system were not included, and so our rate of readmission and mortality rates are underestimated. However, an internal audit of our institutional readmission tracking system has shown that ~80% of all readmissions to any institution are





**Figure 3. Outcomes of patients with an early recurrent myocardial infarction (RMI).**  
**A**, Survival analysis of patients with and without early RMI. \*Time zero for patients with RMI (blue curve) is time of RMI; and time zero for patients without RMI is 90 days after index admission for myocardial infarction. **B**, Survival analysis of patients with early RMI with non-ST-segment-elevation myocardial infarction/ST-segment-elevation myocardial infarction.†Time zero for this analysis is the time of RMI. NSTEMI indicates non-ST-segment-elevation myocardial infarction; RMI, recurrent myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.

captured within our health system.<sup>42</sup> Identification of the initial cohort and the causes of readmission were determined by principal diagnosis billing codes, which may lead to misclassification if the coding was inaccurate. However, the use of administrative data has been shown to be accurate (94%) when compared with clinical medical record review.<sup>43</sup> Furthermore, administrative claims data have also been validated as a reliable resource for prior research studies and government projects.<sup>44,45</sup>

## CONCLUSIONS

Early RMI after an AMI is a life-threatening condition with poor outcomes. The majority of these reinfarctions occur within the initial 2 weeks after discharge indicating that preventive efforts should be initiated during hospitalization and continued upon discharge. Aggressive risk factor management, medication compliance, and effective transition of care may serve as

the vital processes in improving the care of patients with MI.

## ARTICLE INFORMATION

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### Affiliations

Cleveland Clinic Heart, Vascular and Thoracic Institute, Cleveland, OH (R.N., K.K., J.R., M.A., E.B., V.M., A.M.L., S.K., U.N.K.); Cleveland Clinic Heart, Vascular and Thoracic Institute Center for Healthcare Delivery Innovation, Cleveland, OH (R.N., M.J., K.K., C.H., U.N.K.); University Cardiology Associates, Augusta, GA (M.J.); and Saint Luke's Mid America Heart Institute, Kansas City, MO (C.H.).

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### Disclosures

None.

### Supplementary Material

Data S1

Table S1

Figure S1

## REFERENCES

- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139:56–528. DOI: 10.1161/CIR.0000000000000659.
- Bata IR, Gregor RD, Wolf HK, Brownell B. Trends in five-year survival of patients discharged after acute myocardial infarction. *Can J Cardiol*. 2006;22:399–404. DOI: 10.1016/S0828-282X(06)70925-4.
- Montrief T, Davis WT, Koyfman A, Long B. Mechanical, inflammatory, and embolic complications of myocardial infarction: an emergency medicine review. *Am J Emerg Med*. 2019;37:1175–1183. DOI: 10.1016/j.ajem.2019.04.003.
- Dunlay SM, Weston SA, Killian JM, Bell MR, Jaffe AS, Roger VL. Thirty-day rehospitalizations after acute myocardial infarction. *Ann Intern Med*. 2012;157:11–18. DOI: 10.7326/0003-4819-157-1-201207030-00004.
- Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2015;36:1163–1170. DOI: 10.1093/eurheartj/ehu505.
- Forrester AW, Lipsey JR, Teitelbaum ML, Depaulo JR, Andrzejewski PL, Robinson RG. Depression following myocardial infarction. *Int J Psychiatry Med*. 1992;22:33–46. DOI: 10.2190/CJ9D-32C2-8CM7-FT3D.
- Kim LK, Yeo I, Cheung JW, Swaminathan RV, Wong SC, Charitakis K, Adejumo O, Chae J, Minutello RM, Bergman G, et al. Thirty-day readmission rates, timing, causes, and costs after ST-segment-elevation myocardial infarction in the United States: a national readmission database analysis 2010–2014. *J Am Heart Assoc*. 2018;7:009863. DOI: 10.1161/JAHA.118.009863.
- Stone SG, Serrao GW, Mehran R, Tomey MI, Witzensichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Möckel M, et al. Incidence, Predictors, and implications of reinfarction after primary percutaneous coronary intervention in ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*. 2014;7:543–551. DOI: 10.1161/CIRCINTERVENTIONS.114.001360.
- Radovanovic D, Maurer L, Bertel O, Witassek F, Urban P, Stauffer JC, Pedrazzini G, Erne P. Treatment and outcomes of patients with recurrent myocardial infarction: a prospective observational cohort study. *J Cardiol*. 2016;68:498–503. DOI: 10.1016/j.jjcc.2015.11.013.
- Shotan A, Blondheim DS, Gottlieb S, Kazatsker M, Frimerman A, Shochat M, Garty M, Boyko V, Behar S, Meisel SR. Comparison of outcome of recurrent versus first ST-segment elevation myocardial infarction (From National Israel Surveys 1998 to 2006). *Am J Cardiol*. 2011;107:1730–1737. DOI: 10.1016/j.amjcard.2011.02.332.
- Thune JJ, Signorovitch JE, Kober L, McMurray JJV, Swedberg K, Rouleau J, Maggioni A, Velazquez E, Califf R, Pfeffer MA, et al. Predictors and prognostic impact of recurrent myocardial infarction in patients with left ventricular dysfunction, heart failure, or both following a first myocardial infarction. *Eur J Heart Fail*. 2011;13:148–153. DOI: 10.1093/eurjhf/hfq194.
- Nelson S, Whitsel L, Khavjou O, Phelps D, Leib A. Prepared For.; 2016. <https://healthmetrics.heart.org/wp-content/uploads/2017/10/Projections-of-Cardiovascular-Disease.pdf>. Accessed March 20, 2020.
- Blackstone EH, Naftel DC, Turner ME. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615–624. DOI: 10.1080/01621459.1986.10478314.
- Rajeswaran J, Blackstone EH. Identifying risk factors: challenges of separating signal from noise. *J Thorac Cardiovasc Surg*. 2017;153:1136–1138. DOI: 10.1016/j.jtcvs.2017.01.010.
- Mansukhani RP, Bridgeman MB, Candelario D, Eckert LJ. Exploring transitional care: evidence-based strategies for improving provider communication and reducing readmissions. *Pharm Ther*. 2015;40:690–694.
- Kirkham HS, Clark BL, Paynter J, Lewis GH, Duncan I. The effect of a collaborative pharmacist-hospital care transition program on the likelihood of 30-day readmission. *Am J Heal Pharm*. 2014;71:739–745. DOI: 10.2146/ajhp130457.
- Stewart S, Pearson S, Horowitz JD. Effects of a home-based intervention among patients with congestive heart failure discharged from acute hospital care. *Arch Intern Med*. 1998;158:1067. DOI: 10.1001/archinte.158.10.1067.
- Krumholz HM, Amatruda J, Smith GL, Matterna JA, Roumanis SA, Radford MJ, Crombie P, Vaccarino V. Randomized trial of an education and support intervention to prevent readmission of patients with heart failure. *J Am Coll Cardiol*. 2002;39:83–89. DOI: 10.1016/S0735-1097(01)01699-0.
- Leppin AL, Gionfriddo MR, Kessler M, Brito JP, Mair FS, Gallacher K, Wang Z, Erwin PJ, Sylvester T, Boehmer K, et al. Preventing 30-day hospital readmissions. *JAMA Intern Med*. 2014;174:1095. DOI: 10.1001/jamainternmed.2014.1608.
- Howie-Esquivel J, Carroll M, Brinker E, Kao H, Pantilat S, Rago K, De Marco T. A strategy to reduce heart failure readmissions and inpatient costs. *Cardiol Res*. 2015;6:201–208. DOI: 10.14740/cr384w.
- Garnier A, Rouiller N, Gachoud D, Nachar C, Voirol P, Griesser AC, Uhlmann M, Waeber G, Lamy O. Effectiveness of a transition plan at discharge of patients hospitalized with heart failure: a before-and-after study. *ESC Hear Fail*. 2018;5:657–667. DOI: 10.1002/ehf2.12295.
- Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY, Cabrera-Fuentes HA, Hausenloy DJ. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. *Pharmacol Ther*. 2018;186:73–87. DOI: 10.1016/j.pharmthera.2018.01.001.
- Frangogiannis NG. The inflammatory response in myocardial injury, repair and remodeling. *Nat Rev Cardiol*. 2014;11:255–265.
- Wollenweber T, Roentgen P, Schäfer A, Schatka I, Zwadlo C, Brunkhorst T, Berding G, Bauersachs J, Bengel FM. Characterizing the inflammatory tissue response to acute myocardial infarction by clinical multimodality noninvasive imaging. *Circ Cardiovasc Imaging*. 2014;7:811–818. DOI: 10.1161/CIRCIMAGING.114.001689.
- Huang WC, Chou RH, Chang CC, Hsu CY, Ku YC, Huang HF, Chen YC, Huang PH. Systemic inflammatory response syndrome is an independent predictor of one-year mortality in patients with acute myocardial infarction. *Acta Cardiol Sin*. 2017;33:477–485.
- Hamzic-Mehmedbasic A. Inflammatory cytokines as risk factors for mortality after acute cardiac events. *Med Arch*. 2016;70:252–255.
- Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. DOI: 10.1056/NEJMoa1707914.
- ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349–360.
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate

- lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. DOI: 10.1056/NEJMoa040583.
30. Ho PM, Tsai TT, Maddox TM, Powers JD, Carroll NM, Jackevicius C, Go AS, Margolis KL, DeFor TA, Rumsfeld JS, et al. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation. *Circ Cardiovasc Qual Outcomes*. 2010;3:261–266. DOI: 10.1161/CIRCOUTCOMES.109.902031.
  31. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation*. 2008;117:1028–1036. DOI: 10.1161/CIRCULATIONAHA.107.706820.
  32. Anavekar NS, McMurray JJV, Velazquez EJ, Solomon SD, Kober L, Rouleau J-L, White HD, Nordlander R, Maggioni A, Dickstein K, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295. DOI: 10.1056/NEJMoa041365.
  33. Wanamaker BL, Seth MM, Sukul D, Dixon SR, Bhatt DL, Madder RD, Rumsfeld JS, Gurm HS. Relationship between troponin on presentation and in-hospital mortality in patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention. *J Am Heart Assoc*. 2019;8:e013551. DOI: 10.1161/JAHA.119.013551.
  34. Spertus JA, Jones PG, Masoudi FA, Rumsfeld JS, Krumholz HM. Factors associated with racial differences in myocardial infarction outcomes. *Ann Intern Med*. 2009;150:314–324. DOI: 10.7326/0003-4819-150-5-200903030-00007.
  35. Kini V, Peterson PN, Spertus JA, Kennedy KF, Arnold SV, Wasfy JH, Curtis JP, Bradley SM, Amin AP, Ho PM, et al. Clinical model to predict 90-day risk of readmission after acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004788. DOI: 10.1161/CIRCOUTCQUES.118.004788.
  36. McIlvennan CK, Eapen ZJ, Allen LA. Hospital readmissions reduction program. *Circulation*. 2015;131:1796–1803. DOI: 10.1161/CIRCULATIONAHA.114.010270.
  37. Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse remodeling and reverse remodeling after myocardial infarction. *Curr Cardiol Rep*. 2017;19:71. DOI: 10.1007/s11886-017-0876-4.
  38. Bauters C, Dubois E, Porouchani S, Saloux E, Fertin M, de Groote P, Lamblin N, Pinet F. Long-term prognostic impact of left ventricular remodeling after a first myocardial infarction in modern clinical practice. *PLoS One*. 2017;12:e0188884. DOI: 10.1371/journal.pone.0188884.
  39. Hausenloy DJ, Yellon DM. Myocardial ischemia-reperfusion injury: a neglected therapeutic target. *J Clin Invest*. 2013;123:92–100. DOI: 10.1172/JCI62874.
  40. Sheikh AS, Yahya S, Sheikh NS, Sheikh AA. C-reactive protein as a predictor of adverse outcome in patients with acute coronary syndrome. *Heart Views*. 2012;13:7–12. DOI: 10.4103/1995-705X.96660.
  41. Andrié RP, Becher UM, Frommold R, Tiyerili V, Schrickel JW, Nickenig G, Schwab JO. Interleukin-6 is the strongest predictor of 30-day mortality in patients with cardiogenic shock due to myocardial infarction. *Crit Care*. 2012;16:R152. DOI: 10.1186/cc11467.
  42. Khot UN, Johnson MJ, Wiggins NB, Lowry AM, Rajeswaran J, Kapadia S, Menon V, Ellis SG, Goepfarth P, Blackstone EH. Long-term time-varying risk of readmission after acute myocardial infarction. *J Am Heart Assoc*. 2018;7:e009650. DOI: 10.1161/JAHA.118.009650.
  43. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004;148:99–104. DOI: 10.1016/j.ahj.2004.02.013.
  44. Yan Y, Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Comorbidity indices to predict mortality from Medicare data: results from the national registry of atrial fibrillation. *Med Care*. 2005;43:1073–1077. DOI: 10.1097/01.mlr.0000182477.29129.86.
  45. Ramsey SD, Berry K, Etzioni R, Kaplan RM, Sullivan SD, Wood DE; National Emphysema Treatment Trial Research Group. Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med*. 2003;348:2092–2102.

# **SUPPLEMENTAL MATERIAL**

**Data S1. Variables considered in the multivariable analysis.**

**Variables at admission**

Demographic: Age (years), gender, body mass index ( $\text{kg}\cdot\text{m}^{-2}$ ), race  
Ventricular dysfunction: LV ejection fraction (%),  
Cardiac comorbidity: CAD, CHF, HTN, STEMI, N-STEMI  
Noncardiac comorbidity: Diabetes, Smoking, Dyslipidemia, Chronic Kidney disease,  
Dialysis, Creatinine ( $\text{mg}\cdot\text{dL}^{-1}$ ), Lowest HGB, Peak Troponin,  
Peak MB, Peak CK,

***Procedures:*** CABG, PCI, Medically treated

***Variable at discharge***

Noncardiac comorbidity: Hemoglobin, Creatinine ( $\text{mg}\cdot\text{dL}^{-1}$ ),  
Length of Stay: Hospital length of stay during index admission (days)  
Medication: ACE inhibitors, Beta Blockers, P2Y12 inhibitors,  
Anticoagulants, Aldosterone antagonists, ARB, Aspirin,

**Table S1. Parsimonious model: Incremental risk factors for first readmission for MI.**

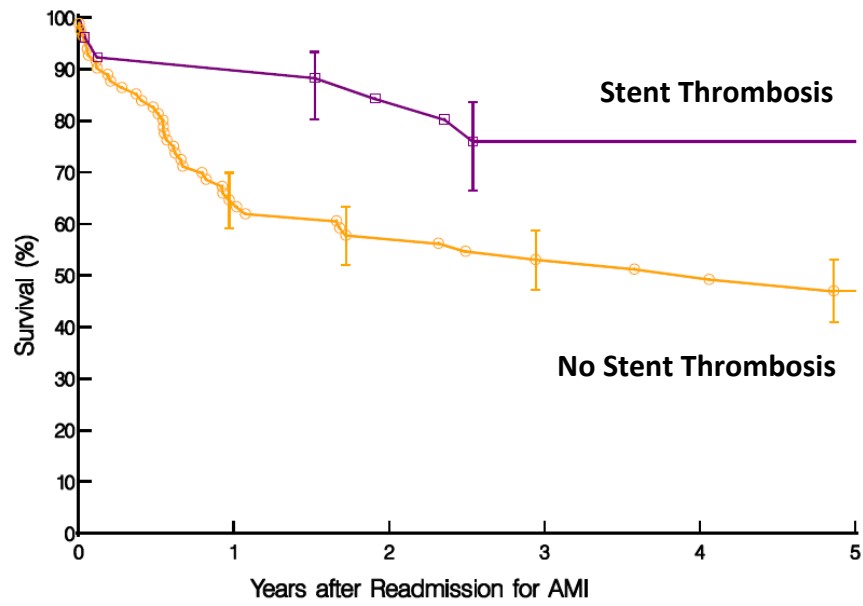
<b>Risk Factor</b>	<i>Coefficient ± SE</i>	<i>P</i>	<i>R (%)</i>
<i>Early hazard phase</i>			
Race: African American	0.58±0.22	.02	48
Higher peak troponin T <sup>#</sup>	0.30±0.089	.0008	77
Treatment: Medically managed	0.88±0.27	.001	63
Shorter index length of stay <sup>‡</sup>	0.45±0.12	.0001	80
<i>Late hazard phase</i>			
Race: African American	0.49±0.25	.05	50
History of CHF	0.62±0.24	.01	62

*R (%)*—bagging reliability— interpreted as the probability of  $P < .05$ , and represents the proportion of 1000 bootstrap analyses in which this variable was retained with  $P < .05$ .

<sup>#</sup>Log [peak troponinT during admission], logarithmic transformation

<sup>‡</sup>[Index admission length of stay], inverse transformation

**Figure S1. Survival Analysis of Patients with and without Stent thrombosis.**



P[Log-rank] =0.06

Survival estimates (%)

Time	No Stent Thrombosis	Stent Thrombosis
1 year	65	92
3 years	53	76
5 years	47	76