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Preadmission Statin Treatment and Outcome in Patients Hospitalized With COVID-19

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Preadmission statin therapy is associated with improved outcome in patients hospitalized with COVID-19. Whether inhibition of inflammation and myocardial injury are in part responsible for this observation has not been studied. The aim of the present study was to relate preadmission statin usage to markers of inflammation, myocardial injury, and clinical outcome among patients with established atherosclerosis who were admitted with COVID-19. Adult patients with a diagnosis of coronary artery disease, peripheral artery disease, and/or atherosclerotic cerebrovascular disease who were hospitalized with COVID-19 between March 1, 2020 and December 31, 2020 were included. Statin use was related to the primary composite clinical outcome, death, intensive care unit admission, or thrombotic complications in sequential multivariable logistic regression models. Of 3,584 adult patients who were hospitalized with COVID-19, 1,360 patients met study inclusion criteria (mean age 73.8 years, 45% women, 68% White). Baseline troponin and C-reactive protein were lower in patients on statins before admission. In an unadjusted model, preadmission statin usage was associated with a significant reduction in the primary composite outcome (42.2% vs 53.7%, odds ratio 0.63 [95% confidence interval 0.50 to 0.80], p <0.001). This association remained significant after age, gender, ethnicity, other patient clinical characteristics, and cardiovascular medications were added to the model but became null when troponin and C-reactive protein were also included (odds ratio 0.83 [95% confidence interval 0.63 to 1.09] p = 0.18). In conclusion, among patients with established cardiovascular disease who were hospitalized with COVID-19, preadmission statin therapy was associated with improved in-hospital outcome, an association that was negated once inflammation and myocardial injury were considered. **(Am J Cardiol 2022;177:28−33)**

COVID-19, caused by SARS-CoV-2, has been associated with significant morbidity and mortality, mainly mediated through an intense inflammatory host response with resultant respiratory and multiorgan failure.[1] Elevation of biomarkers, reflecting inflammation and myocardial injury, predict poorer outcome in patients with COVID-19.[2−4] Statins possess antiviral, immunomodulatory, antithrombotic, and anti-inflammatory properties[5] and reduce inflammation and myocardial injury in patients with atherosclerotic vascular disease,[6] properties which may translate into improved short- and long-term outcomes in these patients.[7,8] Observational studies of patients hospitalized with COVID-19 have found that preadmission statin use is associated with less inflammation, less severe disease manifestations, and improved outcomes;[9,10] whether statins reduce myocardial injury in this setting is unknown. The present study examined whether markers of inflammation and myocardial injury modify the relation between preadmission statin use and clinical outcome in patients hospitalized with COVID-19.

Methods

Baseline demographic, clinical, medication, laboratory, and outcome data were extracted electronically from the EPIC Systems electronic health record. All consecutive patients aged ≥18 years, with a diagnosis of coronary artery disease, peripheral artery disease, and/or atherosclerotic cerebrovascular disease who were hospitalized with COVID-19 at Rhode Island, the Miriam or Newport Hospitals, between March 1, 2020 and December 31, 2020 were included. Co-morbidities, COVID-19 status, and in-hospital outcomes were ascertained using International Classification of Diseases, Tenth Revision codes (Supplementary Material). Approval and waiver of informed consent were granted by the Miriam Hospital Institutional Review Board.

Statin use was ascertained from home and inpatient medication lists. Statins were categorized by agent, dose, intensity,[11] and solubility. If 2 statins were listed, the higher intensity statin took precedence and was included in the descriptive table; patients in whom both a lipophilic and hydrophilic statin were listed were excluded from the descriptive statistics on statin solubility.

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See page 32 for disclosure information.

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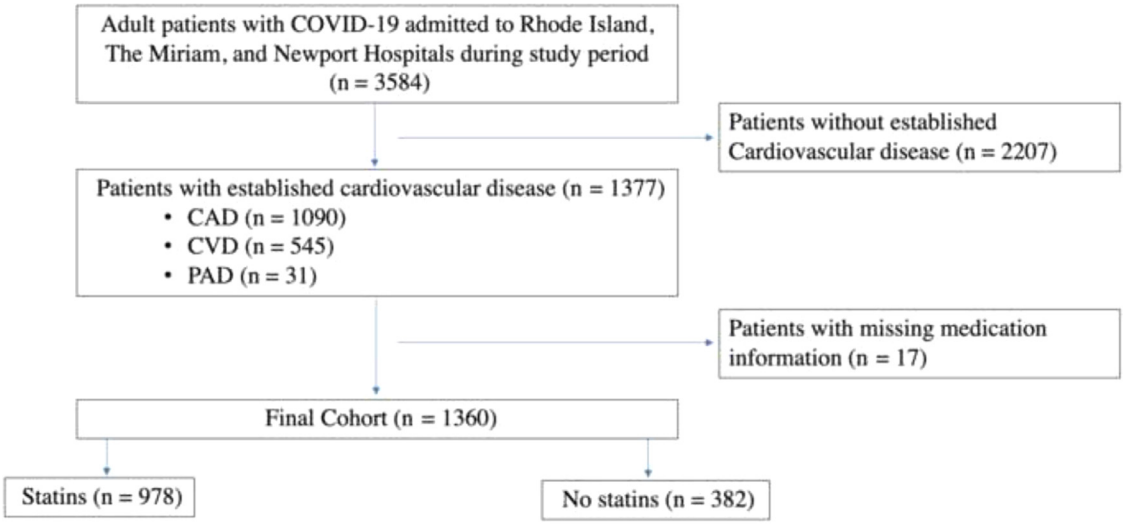

Figure 1. Study flowchart. CAD = coronary artery disease; CVD = cerebrovascular disease; PAD = peripheral artery disease.

The primary composite outcome included in-hospital death, intensive care unit (ICU) admission, or composite thrombotic complications. Secondary clinical outcomes included individual components of the primary composite outcome, composite death or ICU admission, individual thrombotic complications, and length of stay. Baseline levels of inflammation and myocardial injury were gauged by C-reactive protein (CRP) and cardiac troponin I levels on admission, respectively (Supplementary Material).

Continuous variables are presented as means ± SD or medians with interquartile range (IQR) and were compared using the Student *t* test or Wilcoxon rank-sum test, as appropriate. Categoric variables are presented as frequencies and percentages and were compared using the chi-square test.

Preadmission statin use was related to the primary composite clinical outcome in unadjusted and adjusted analyses. Plausible demographic, clinical characteristics, and cardiovascular medications that were related to the primary outcome ($p \leq 0.15$) were eligible for inclusion in multivariable models and are detailed in Supplementary Material. Analyses were performed using sequential multivariable logistic regression models, as follows: (1) unadjusted; (2) model 1 + age, gender, and ethnicity; (3) model 2 + other patient characteristics; (4) model 3 + other cardiovascular medications, and (5) model 4 + CRP and troponin. Patients with missing information regarding preadmission medication use were excluded (n = 17). Missing troponin (10%) and CRP (19%) values were imputed using simple imputation techniques (IVEware, Ann Arbor, Michigan). All analyses were performed with SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

A study flow diagram appears in Figure 1. Of 3,584 adult patients hospitalized with COVID-19, 1,377 had established atherosclerotic cardiovascular disease. The final study cohort comprised 1,360 patients; of these, 1,090 patients (80%) had coronary artery disease, 545 patients (40%) had cerebrovascular disease, and 31 patients (2%) had peripheral artery disease. Patient characteristics according to preadmission statin use appear in Table 1. Overall mean age was 73.8 ± 13.7 years, 45% were women, and 67.6% were White. Cardiovascular risk factors and risk markers were common. Half of the patients were taking β blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and nearly 2/3 were taking antiplatelet agents before admission.

In the overall cohort, 978 patients (72%) were taking statins before admission (2 statins were listed for 28 of these). Statin use was significantly more common among those with hypertension, diabetes, obesity, previous myocardial infarction (MI) or percutaneous coronary intervention, and among nonsmokers. Atorvastatin was the most commonly used (n = 675, 69%). Statin use details appear in Table 2 and in Supplementary Material. Of those on preadmission statins, these agents were discontinued during hospitalization in 153 patients (16%); in contrast, of those not on preadmission statins, these agents were initiated in 57 (15.5%) during hospitalization. Patients who were taking statins before admission had lower median (IQR) troponin (0.055 [0.018 to 0.23] vs 0.090 [0.02 to 0.37] ng/ml, p = 0.001) and CRP (64.9 [27.0 to 134.3] vs 76.1 [27.0 to 156.0] mg/L, p = 0.008) at baseline compared with those not on statins. Patients who were taking high/intermediate-intensity statins before admission had lower median (IQR) troponin (0.051 [0.017 to 0.22] vs 0.086 [0.026 to 0.27] ng/ml, p = 0.035) but similar median (IQR) CRP (72.8 [30.7 to 136.7] vs 102.2 [36.0 to 169.9] mg/L, p = 0.14) at baseline compared with those not on low-intensity statins.

The primary composite outcome occurred in 618 patients (45%). In an unadjusted analysis, preadmission statin usage was associated with a significantly lower incidence of the primary composite outcome (413 [42.2%] vs 205 [53.7%], odds ratio [OR] 0.63 [95% confidence interval (CI) 0.50 to 0.80], p <0.001). This association remained significant after sequential adjustment (model 2 OR 0.65 [95% CI 0.51 to 0.83], p <0.001; model 3 OR 0.75 [95% CI 0.58 to 0.99], p = 0.039; and model 4 OR 0.75 [95% CI

Table 1
Baseline characteristics

Variable	Total (n = 1360)	Statin therapy		P-value
		Yes (n = 978)	No (n = 382)	
Age (years), mean ± SD	73.8 ± 13.7	74.8 ± 11.7	71.3 ± 17.4	< 0.001
Female	614 (45.1%)	432 (44.2%)	182 (47.6%)	0.25
Hispanic or Latino	233 (17.1%)	170 (17.4%)	63 (16.5%)	0.34
Not Hispanic or Latino	1116 (82.1%)	802 (82.0%)	314 (82.2%)	
Unknown	1 (0.1%)	0 (0.0%)	1 (0.3%)	
White	919 (67.6%)	665 (68.0%)	254 (66.5%)	0.66
Asian	19 (1.4%)	15 (1.5%)	4 (1.0%)	
Black	173 (12.7%)	119 (12.2%)	54 (14.1%)	
Native Hawaiian/other Pacific Islander	3 (0.2%)	3 (0.3%)	0 (0.0%)	
Other	236 (17.4%)	170 (17.4%)	66 (17.3%)	
Unknown	10 (0.7%)	6 (0.6%)	4 (1.0%)	
Hypertension	1193 (87.7%)	901 (92.1%)	292 (76.4%)	< 0.001
Obesity	375 (27.6%)	289 (29.6%)	86 (22.5%)	0.009
Smoker				< 0.001
Current	109 (8.0%)	73 (7.5%)	36 (9.4%)	
Former	562 (41.3%)	454 (46.4%)	108 (28.3%)	
Never	528 (38.8%)	365 (37.3%)	163 (42.7%)	
Unknown	161 (11.8%)	86 (8.8%)	75 (19.6%)	
Diabetes mellitus	662 (48.7%)	533 (54.5%)	129 (33.8%)	< 0.001
Previous coronary artery disease	1088 (80.0%)	800 (81.8%)	288 (75.4%)	0.007
Previous cerebrovascular disease	253 (20.8%)	177 (20.0%)	76 (22.7%)	0.31
Previous peripheral artery disease	26 (2.1%)	18 (2.0%)	8 (2.4%)	0.70
Previous percutaneous coronary intervention	222 (16.3%)	197 (20.1%)	25 (6.5%)	< 0.001
Previous coronary artery bypass grafting	96 (7.1%)	85 (8.7%)	11 (2.9%)	< 0.001
Previous myocardial infarction	312 (22.9%)	268 (27.4%)	44 (11.5%)	< 0.001
Previous transient ischemic attack/stroke	312 (22.9%)	242 (24.7%)	70 (18.3%)	0.011
Heart failure	499 (36.7%)	376 (38.4%)	123 (32.2%)	0.031
Valvular heart disease	122 (9.0%)	94 (9.6%)	28 (7.3%)	0.18
Cardiac dysrhythmias	626 (46.0%)	458 (46.8%)	168 (44.0%)	0.34
Chronic kidney disease	355 (26.1%)	275 (28.1%)	80 (20.9%)	0.006
Chronic obstructive pulmonary disorder	175 (12.9%)	128 (13.1%)	47 (12.3%)	0.70
Obstructive sleep apnea	155 (11.4%)	124 (12.7%)	31 (8.1%)	0.017
Liver disease	128 (9.4%)	79 (8.1%)	43 (11.3%)	0.06
Dementia	402 (29.6%)	275 (28.1%)	127 (33.2%)	0.06
Cancer	151 (11.1%)	108 (11.0%)	43 (11.3%)	0.91
Inflammatory rheumatic disease	200 (14.7%)	145 (14.8%)	55 (14.4%)	0.84
Cardiac troponin, ng/ml, median (IQR)	0.065 (0.02, 0.25)	0.055 (0.02, 0.23)	0.090 (0.02, 0.37)	0.001
C-reactive protein, mg/L, median (IQR)	68.6 (27.0, 139.5)	64.9 (27.0, 134.3)	76.1 (27.0, 156.0)	0.008
Preadmission medications, n (%)				
Nonstatin anticholesterol agent	104 (7.6%)	78 (8.0%)	26 (6.8%)	0.46
Renin-angiotensin-aldosterone system inhibitors	684 (50.3%)	537 (54.9%)	147 (38.5%)	< 0.001
Beta blocker	687 (50.5%)	546 (55.8%)	141 (36.9%)	< 0.001
Antiplatelet agent	812 (59.7%)	682 (69.7%)	130 (34.0%)	< 0.001

0.57 to 0.99], p = 0.04). However, in model 4, when troponin and CRP were also included, the association between preadmission statin ue and the primary outcome was further attenuated and no longer significant (OR 0.83 [95% CI 0.63 to 1.09] p = 0.18) (Figure 2). Unadjusted secondary outcomes appear in Table 3. Compared with those who were not taking statins before admission, preadmission statin use was associated with significant reduction in thrombotic complications and lengths of stay. In-hospital all-cause mortality and composite death or ICU admission occurred less frequently in those on preadmission statins, but these differences were not statistically significant.

Discussion

In a retrospective analysis of patients with established atherosclerotic cardiovascular disease who were hospitalized with COVID-19, preadmission statin usage was associated with a lower incidence of composite in-hospital death, ICU admission, or thrombotic complications. This association persisted despite sequentially adjusting for demographics, clinical characteristics, and other cardiovascular medications but became null after including baseline CRP and troponin levels, suggesting that the observed association between preadmission statin use and clinical outcome

Table 2
Statin usage

Statin intensity*	
Low	91 (6.7%)
Intermediate	409 (30.1%)
High	506 (37.2%)
Statin solubility†	
Lipophilic	824 (84.3%)
Hydrophilic	172 (17.6%)
Statin agent	
Atorvastatin	675 (69.0 %)
Simvastatin	108 (11.0 %)
Pravastatin	87 (8.9 %)
Rosuvastatin	68 (7.0 %)
Lovastatin	39 (4 %)
Pitavastatin	1 (0.1 %)

* Classification of statin intensity by agent and dose is presented in Supplemental Material.

† Classification of statin lipophilicity by agent is presented in Supplemental Material.

may have been mediated, in part, by reductions in inflammation and/or myocardial injury.

Elevated troponin, even at low levels, portends a poorer outcome in patients with COVID-19. Even minor myocardial injury is associated with significant increase in mortality,[12] more severe respiratory illness, and greater likelihood of composite death, intubation, need for critical care, or cardiac arrest.[13] The pathophysiology underlying myocardial injury in patients with acute viral infection is multifactorial and may involve inflammatory, prothrombotic, and procoagulant cascades.[4,14] Markers of these pathways have been observed in high concentrations in patients with severe multisystem COVID-19 illness and "cytokine storm".[15] The activation of these cascades can also promote coronary plaque instability and acute thrombosis, resulting in type 1 MI.[4] Critical illness, sepsis, hypoxemia, acidosis, and hypotension may result in supply-demand mismatch and consequent type 2 MI.[14,16] Nonischemic myocardial injury may also result from direct injury to myocytes by SARS-CoV-2 through angiotensin-converting enzyme 2 receptors.[17] The ability of statin treatment to ameliorate myocardial injury has been established in other settings.[18]

Patients with COVID-19 and elevated inflammatory markers (i.e., hyperinflammatory response) have poorer outcome, including greater need for oxygen supplementation, mechanical ventilation, and extracorporeal membrane oxygenation and higher mortality than those in a hypoinflammatory response.[15,19] Dysregulation of angiotensin signaling resulting from SARS-COV-2 and angiotensin-converting enzyme 2 receptor interaction leads to proinflammatory cytokine release and promotes platelet activation, which in turn releases other proinflammatory factors, culminating in a cascade of inflammation and thrombosis.[20] It is possible that statin-driven benefits are linked to anti-inflammatory and immunomodulatory effects through lipid raft disruption; inhibition of the nuclear factor kappa-light-enhancer pathway; and suppression of cytokines, chemokines, and CRP.[21,22] In the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction-2 Study, simvastatin was associated with improved survival in the hyperinflammatory subphenotype of adult respiratory distress syndrome compared with placebo.[23]

There are conflicting data regarding the association between preadmission statin use and outcome in patients with COVID-19, although when meta-analyzed,

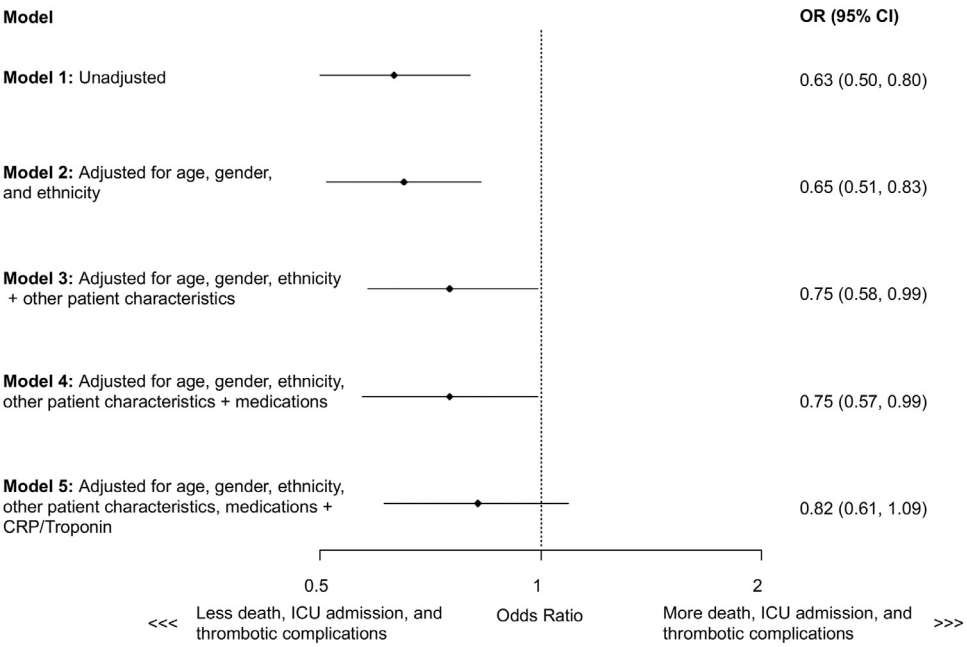

Figure 2. Forrest plot summarizing unadjusted and sequential multivariable logistic regression models. Demographic and clinical characteristics considered for inclusion in multivariable models were demographics (age, gender, ethnicity), clinical characteristics (smoking, obesity, hypertension, previous myocardial infarction, previous cerebrovascular disease, previous cardiac arrhythmias, pulmonary circulatory disorders, liver disease), cardiovascular medications (β blockers, renin-angiotensin-aldosterone system inhibitors, antiplatelets).

Table 3
Secondary outcomes

Outcome	Total (n = 1360)	Statin therapy		P-value
		Yes (n = 978)	No (n = 382)	
Death	265 (19.5%)	183 (18.7%)	82 (21.5%)	0.25
Death or admission to intensive care unit	411 (30.2%)	281 (28.7%)	130 (34.0%)	0.06
Composite thrombotic complications*	363 (26.7%)	235 (24.0%)	128 (33.5%)	<0.001
Stroke/TIA	137 (10.1%)	83 (8.5%)	54 (14.1%)	0.001
ACS	156 (11.5%)	101 (10.3%)	55 (14.4%)	0.034
Acute DVT/PE	98 (7.2%)	67 (6.9%)	31 (8.1%)	0.42
Acute mesenteric ischemia	2 (0.1%)	2 (0.2%)	0 (0.0%)	0.38
Acute limb ischemia	19 (1.4%)	12 (1.2%)	7 (1.8%)	0.39
Length of stay, median (IQR)	6.0 (4.0, 13.0)	6.0 (4.0, 12.0)	7.0 (4.0, 14.0)	0.002

* Composite thrombotic complications: myocardial infarction, ischemic cerebrovascular accident, venous thromboembolism, acute limb ischemia, and acute mesenteric ischemia.

ACS = acute coronary syndrome; MI = myocardial infarction; TIA = transient ischemic attack, DVT = deep venous thrombosis, PE = pulmonary embolism.

preadmission statin therapy is associated with more favorable outcomes.[10] Our results are congruent with these aggregated findings, and our observation that statins are associated with less myocardial injury and fewer thrombotic complications in this setting is novel. To our knowledge, our study is the first to account for markers of inflammation and myocardial injury in sequential multivariable logistic regression models and to suggest that the improved outcomes associated with upstream statin use in patients who were hospitalized with COVID-19 may be related to lesser degrees of myocardial injury and/or inflammation. This observation is biologically plausible, especially because data suggest early activation of thrombosis and inflammatory cascades with SARS-COV-2 infection.[24,25] In preliminary findings from the INSPIRATION-S study of critically ill patients with COVID-19, the composite outcome, arterial and venous thrombosis, use of extracorporeal membrane oxygenation, or 30-day death occurred numerically less often in atorvastatin than placebo-treated groups, but these differences were not statistically significant.[26,27] However, an interaction between treatment assignment and duration of symptoms was of marginal statistical significance, raising the possibility that treatment initiation closer to symptom onset (i.e., before admission) when inflammation is less pronounced might have conferred benefit. Given that the mean time from symptoms to hospitalization with COVID-19 is approximately 6 days,[28] and that statin-induced reductions in CRP and troponin are evident in 1 and 7 days,[29] respectively, initiation of statin therapy among naïve patients with COVID-19 could potentially translate into lower levels of inflammation and myocardial injury and reduce the likelihood of clinical deterioration. Although randomized trials are examining the role of statin therapy in patients with COVID-19, most have included patients only after they are hospitalized.[21] Only 1 small ongoing trial is evaluating upstream statin therapy in ambulatory patients with COVID-19, but that trial is designed to assess changes in viral load and CRP and is likely underpowered to identify statin-mediated differences in secondary clinical outcomes.[30]

There are noteworthy limitations to our study. First, by restricting our cohort to those with clinically manifest atherosclerotic vascular disease, we attempted to minimize the likelihood of confounding by indication; however, we cannot exclude potential sources of residual confounding, despite multivariable modeling of the primary composite outcome. Second, we used International Classification of Diseases, Tenth Revision codes to define clinical outcomes; resultant, under-, or miscoding may have introduced inaccuracies in our data; although, if that were the case, it would likely have biased our results toward the null. Third, preadmission statin use was confirmed through medication reconciliation by patient report at the time of admission; pharmacy data, which indicated whether prescribed statins were dispensed or refilled, were not available. Fourth, our results may not be generalizable to the primary prevention setting. Finally, only in-hospital clinical outcomes were ascertained; whether preadmission statin use is associated with more favorable long-term outcomes after COVID-19 is unknown.

In conclusion, among patients with established atherosclerotic cardiovascular disease hospitalized with COVID-19, preadmission statin therapy was associated with improved in-hospital outcome; this association was no longer significant after markers of inflammation and myocardial injury were considered, suggesting that the observed association may be mediated through upstream suppression of these phenomena.

Disclosures

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.04.045.

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