Impact of High-Density Lipoprotein Levels on Cardiovascular Outcomes of Patients Undergoing Percutaneous Coronary Intervention With Drug-Eluting Stents

Anastasios Roumeliotis, MD, Bimmer Claessen, PhD, George Dangas, PhD, Rebecca Torguson, MPH, Samantha Sartori, PhD, Adam Reisman, MD, Davide Cao, MD, Rishi Chandiramani, MD, Johny Nicolas, MD, Ridhima Goel, MD, Mauro Chiarito, MD, Madhav Sharma, MD, Dhrubajyoti Bandyopadhyay, MD, Usman Baber, MD, Joseph Sweeny, MD, Nitin Barman, MD, Samin Sharma, MD, Annapoorna Kini, MD, and Roxana Mehran, MD*

Low levels of high-density lipoprotein (HDL) have been associated with adverse cardiovascular events in epidemiologic studies. Evidence regarding its role in patients who underwent percutaneous coronary intervention (PCI) is scarce. We evaluated consecutive patients who underwent PCI with drug-eluting stents from 2012 to 2017, excluding those with unavailable baseline HDL, age <18 years, presentation with ST-segment elevation myocardial infarction (MI) or shock, and coexisting neoplastic disease. The final population was stratified according to baseline HDL levels into reduced and nonreduced HDL cohorts, with cut-off value 40 mg/dl in males and 50 mg/dl in females. The primary end point was 1-year major adverse cardiovascular events (MACE), defined as the composite of death, MI, or target vessel revascularization (TVR). Among 10,843 patients included, 6,511 (60%) had reduced HDL, and 4,332 (40%) nonreduced HDL. The rate of 1-year MACE was similar between the 2 groups (7.5% vs 6.6%; p = 0.14). Although mortality and MI rates were comparable, reduced HDL was associated with significantly higher TVR 5.2% vs 4.0%; p = 0.02, a finding that attenuated after multivariable adjustment (adjusted hazard ratio 1.18, p = 0.14). Sex subgroup analysis included 7,718 (71.2%) males and 3,125 (28.8%) females. Among men, there was a trend toward higher MACE in those with reduced HDL (7.4% vs 6.0%; p = 0.08) mostly driven by TVR (5.4% vs 3.7%; p = 0.005). No association between HDL and 1-year outcomes was evident in females. Assessment for interaction between sex and reduced HDL did not reach statistical significance. In conclusion, reduced baseline HDL was not associated with increased risk of MACE in a contemporary PCI population. **(Am J Cardiol 2020;137:1−6)**

Since the Framingham Study, high levels of high-density lipoprotein (HDL) have been associated with improved cardiovascular outcomes in the general population.[1] Subsequent evidence suggested that properly functioning HDL molecules may contribute to cholesterol uptake from peripheral tissues (reverse cholesterol transport), as well as possess anti-inflammatory and antioxidant properties.[2−4] However, patients enrolled in the ILLUMINATE and dal-OUTCOMES trials failed to obtain benefit despite the significant enhancement of HDL levels achieved by selectively targeted therapy.[5,6] This raised controversy regarding the actual role of HDL in patients already diagnosed or at high risk for coronary artery disease (CAD). Additionally, although females are known to have higher HDL levels, sex-specific effects have not been well described. The purpose of this analysis was to assess the impact of baseline HDL in a cohort of patients who underwent percutaneous coronary intervention (PCI) with drug-eluting stents and to further investigate differential effects of HDL levels on outcomes in males and females.

Methods

We used deidentified data from the catheterization laboratory of a tertiary medical center (The Mount Sinai Hospital, New York, New York) in a retrospective fashion. Baseline clinical, demographic, procedural, and discharge information were prospectively collected along with 1-year outcomes according to our standard hospital database procedure. The registry was approved by the local institutional review board and patient follow-up was carried out by qualified, independent research coordinators.

All patients who underwent PCI from January 1, 2012 to December 31, 2017 who had an available baseline HDL level were considered for inclusion. Exclusion criteria were: age <18 years, presentation with ST-segment elevation

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See page 6 for disclosure information.

*Corresponding author: Tel: (212) 659-9649; fax: (212) 241-0273.
E-mail address: roxana.mehran@mountsinai.org (R. Mehran).

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myocardial infarction or shock, coexisting neoplastic disease, and treatment without a stent or with a bare metal stent. The final population was stratified according to HDL levels into reduced and nonreduced HDL groups. HDL level cut-off values were <40 mg/dl in males and <50 mg/dl in females, per the criteria of the metabolic syndrome referenced in most recent American College of Cardiology/American Heart Association guideline recommendations.[7] Abbott Laboratories commercial kit and analyzer (Architect C16000, Abbott Laboratories, Abbott Park, IL) was utilized for the measurements in the hospital clinical laboratory per standard of care. The prespecified primary outcome of the analysis was major adverse cardiac events (MACE) at 1-year: composite of death, nonperiprocedural myocardial infarction (MI), and target vessel revascularization (TVR). Secondary outcomes were the individual components of MACE as well as target lesion revascularization (TLR) at 1-year follow-up. Comparisons for the different end points were also performed by sex category.

Descriptive statistics are reported as mean ± SD, or percentage when appropriate. The chi-square test was used to compare differences between categorical variables whereas the independent-samples Student's *t* test was used to compare continuous variables. Time-to-event analyses were performed using the Kaplan-Meier method and compared using the log-rank test. To account for potential confounders, the results were adjusted using Cox proportional hazards regression and presented as adjusted hazard ratio and 95% confidence interval. The adjustment model included age, sex, Caucasian ethnicity, hypertension, diabetes mellitus, body mass index, current smoking, prior MI, multivessel disease, and type B2/C lesions. The analyses were performed using Stata version 15.1 (StatCorp, College Station, TX) and a 2-sided p value of <0.05 was considered statistically significant.

Results

The final analysis population comprised of 10,843 patients who underwent PCI, of whom 6,511 (60%) had reduced HDL and 4,332 (40%) had nonreduced HDL. The reduced and nonreduced HDL subgroups demonstrated significantly dissimilar baseline features. Patients with nonreduced HDL were older, mostly white, and more likely to present with non−ST-segment elevation myocardial infarction, whereas those with reduced HDL suffered from a greater burden of co-morbidities such as diabetes, dyslipidemia, and hypertension, and had a higher incidence of multivessel disease (Table 1). The dichotomized HDL groups were similar in terms of statin use on admission had an equivalently high percentage of patients discharged on statin therapy. In males, 58.5% had baseline HDL levels below 40 mg/dl whereas in females, 63.8% had baseline HDL levels below 50 mg/dl. The demographic and baseline differences within the overall population were similar in male and female sex subgroups as depicted in Supplementary Tables 1 and 2, respectively.

When comparing patients with reduced HDL to those with nonreduced HDL, no notable difference was demonstrated concerning the primary end point of 1-year MACE (Figure 1). Additionally, rates of 1-year death and 1-year MI were also constant regardless baseline HDL levels, but a significant reduction was shown in the nonreduced HDL

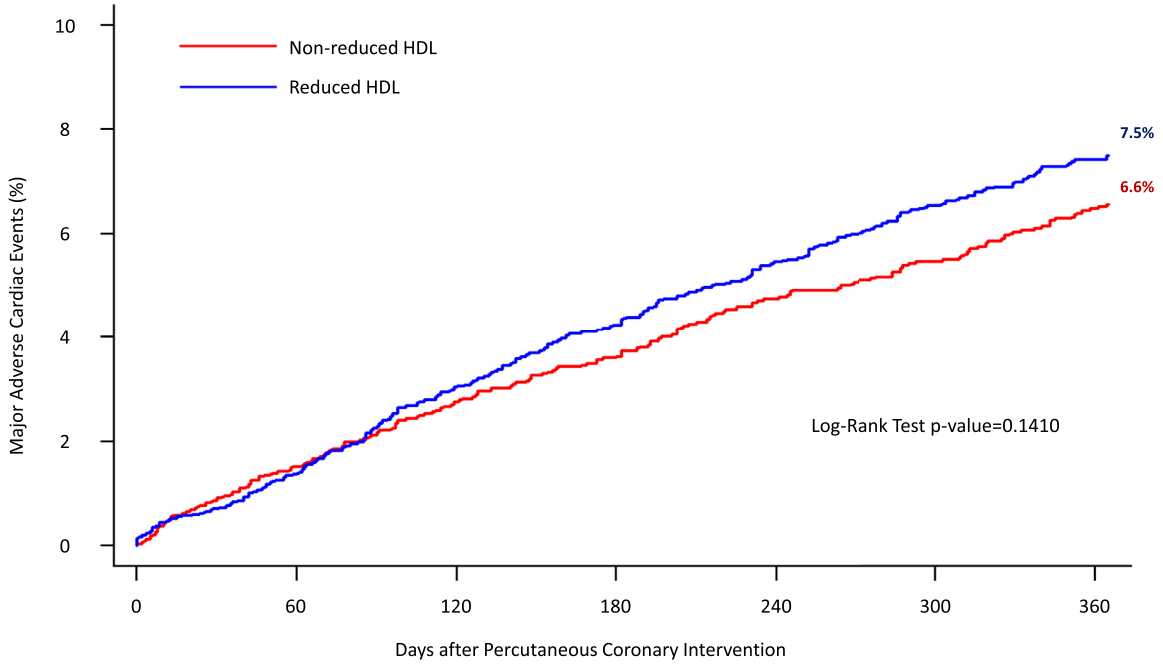


Figure 1. Kaplan-Meier curves comparing nonreduced and reduced HDL subgroups in the overall study population: 1-year MACE. HDL = high-density lipoprotein; MACE = major adverse cardiac events.

Table 1
Demographic, clinical, and procedural characteristics of the general population

Variable	High-density lipoprotein cholesterol		p value
	Reduced (n = 6,511)	Not reduced (n = 4,332)	
Age	64.3 ± 11.1	67.1 ± 11.0	<0.01
Women	30.6%	26.1%	<0.01
White	49.4%	58.3%	<0.01
Body mass index (kg/m^2)	29.5 ± 5.6	28.1 ± 5.5	<0.01
Hyperlipidemia*	94.3%	91.1%	<0.01
Family history of coronary artery disease	26.0%	23.8%	<0.01
Hypertension	93.8%	90.1%	<0.01
Diabetes mellitus	53.6%	39.2%	<0.01
Peripheral arterial disease	9.0%	7.9%	0.05
Prior cerebrovascular accident	9.9%	9.2%	0.22
Chronic kidney disease	25.8%	25.1%	0.43
Smoking	15.1%	10.9%	<0.01
Prior myocardial infarction	22.6%	18.8%	<0.01
Prior coronary artery bypass grafting	16.7%	15.2%	0.04
Total cholesterol (mg/dl)	137.8 ± 39.8	149.8 ± 37.3	<0.01
Low-density lipoprotein (mg/dl)	81.0 ± 32.4	81.7 ± 31.9	0.23
High-density lipoprotein (mg/dl)	34.0 ± 6.3	52.2 ± 10.9	<0.01
Hemoglobin (g/dl)	13.0 ± 1.7	13.1 ± 1.6	<0.01
Platelet	203.3 ± 63.9	196.0 ± 63.4	<0.01
Glucose	132.0 ± 58.3	129.0 ± 67.8	0.08
Creatinine	1.2 ± 1.3	1.2 ± 1.1	0.21
Max stent diameter	3.1	3.1	<0.01
Total stent length	33.5	32.1	<0.01
Number of stents	1.45 ± 0.7	1.41 ± 0.7	<0.01
B2C lesion	73.5%	70.6%	0.01
Multivessel coronary artery disease	67.1%	61.9%	<0.01
Calcification (mod or severe)	21.4%	25.2%	<0.01
Chronic total occlusion	7.3%	7.0%	0.50
Left ventricular ejection fraction	55.7 ± 9.1	55.7 ± 8.9	0.75
Left main	4.4%	4.6%	0.73
Left anterior descending	47.5%	48.8%	0.19
Left circumflex	33.1%	32.0%	0.26
Right coronary artery	29.3%	27.0%	<0.01
Unstable angina	33.5%	30.5%	<0.01
Non−ST-segment elevation myocardial infarction	8.7%	9.9%	0.03
Discharge medication			
Aspirin	97.4%	96.6%	0.02
Clopidogrel	74.4.%	77.1%	<0.01
Prasugrel	9.8%	10.1%	0.69
Ticagrelor	15.8%	12.6%	<0.01
Beta blocker	85.0%	78.6%	<0.01
Statin	94.9%	94.7%	0.72

* History of diagnosed dyslipidemia and/or treated by physician.

subgroup with respect to 1-year TVR and 1-year TLR (Supplementary Table 3). After adjusting for potential confounders, all differences were attenuated (Figure 2).

No statistically significant difference in 1-year MACE was shown for nonreduced versus reduced HDL in either sex. However, a trend toward increased 1-year MACE in the reduced HDL subgroup (7.4% vs 6.0%; p = 0.08) was demonstrated in males (Figure 3). This difference was primarily driven by TVR whereas other components of MACE, specifically death and MI, did not differ (Supplementary Table 4). No association between HDL levels and 1-year outcomes was seen in females (Supplementary Table 5). These results remained qualitatively similar after adjusting (Table 2). When assessing for the interaction between male sex and reduced HDL these 2 covariates did not reach statistical significance in terms of MACE (adjusted p interaction = 0.26), but a trend was shown with regards to TVR (adjusted p interaction = 0.09).

Discussion

The main findings in this contemporary cohort of patients who underwent PCI with drug-eluting stents were: (1) The prevalence of reduced HDL was high among patients, (2) There was no difference in terms of the primary end point of 1-year MACE in the general population before or after adjustment, (3) After stratifying for sex, a decreased rate of 1-year TVR along with a borderline lower

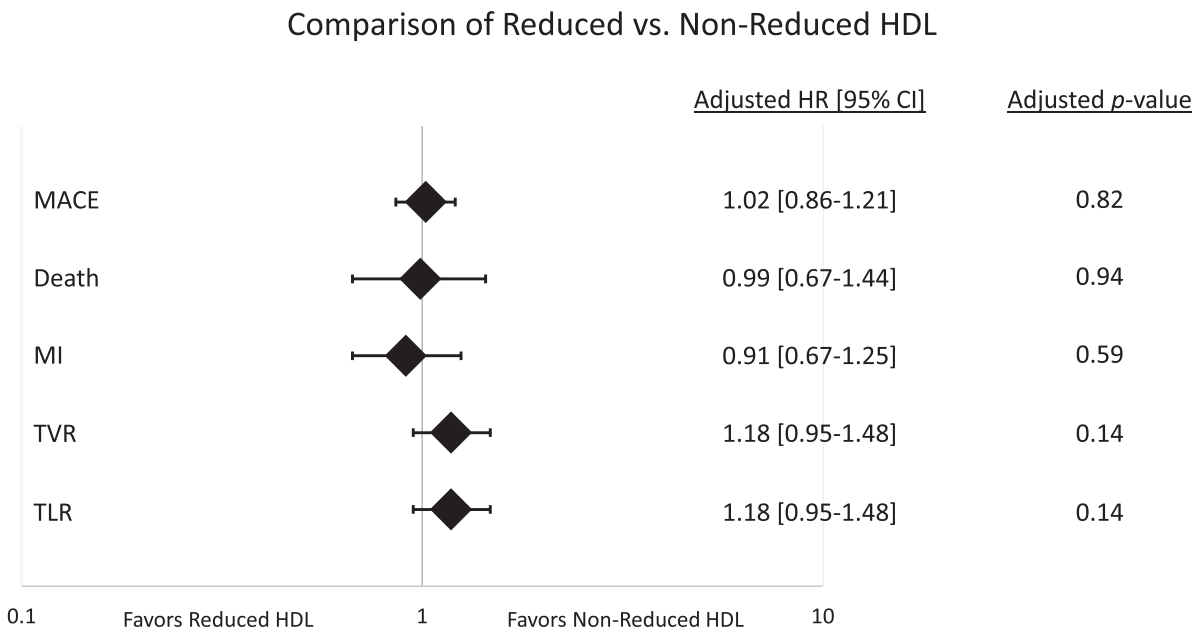
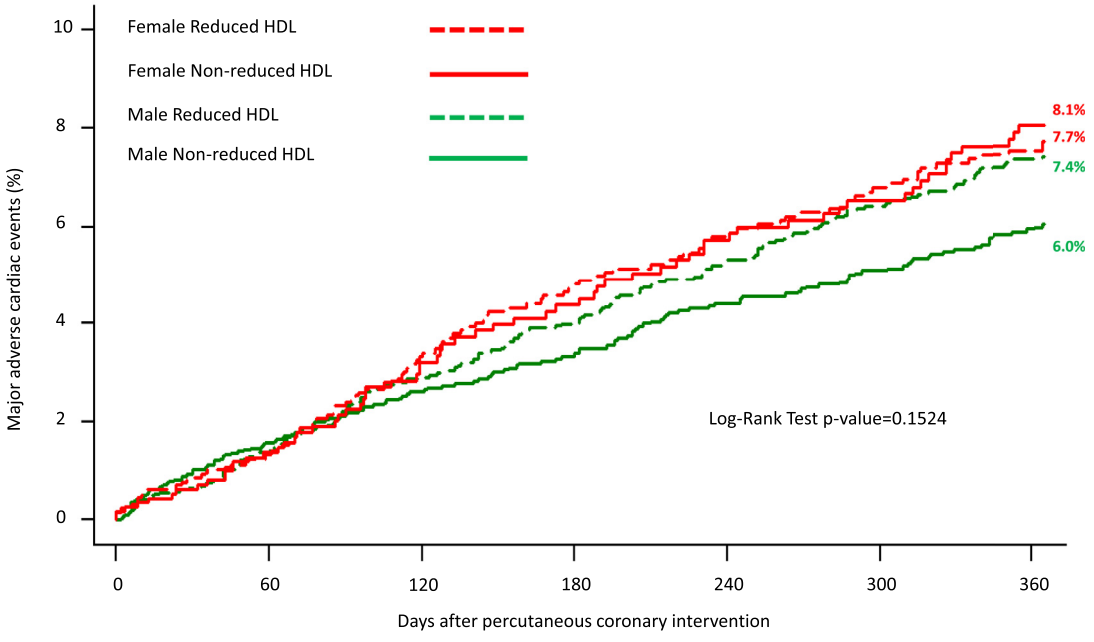


Figure 2. Adjusted hazard ratios comparing the nonreduced and reduced HDL subgroups for different outcome measures in the overall population. The variables used for adjustment were: age, Caucasian ethnicity, hypertension, diabetes mellitus (DM), body mass index, smoking, prior MI, multivessel disease, and type B2/C lesions. HDL = high-density lipoprotein; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

rate of 1-year MACE was evident in the nonreduced HDL subgroup in male patients, but not in female patients, (4) The reduced rate of 1-year TVR in nonreduced HDL (vs reduced HDL) in male patients was maintained even after adjusting for possible confounders.

Although reduced HDL is a component of metabolic syndrome[8] and a well-established predictor of adverse cardiovascular prognosis,[9] recently this relation has been questioned within patients with established CAD.[10] Moreover, medications specifically targeting (raising) HDL levels



Number at risk							
Female Reduced HDL	1131	981	765	723	702	686	623
Female Non-reduced HDL	1994	1724	1278	1175	1148	1123	1015
Male Reduced HDL	3202	2863	2226	2067	1994	1966	1813
Male Non-reduced HDL	4514	3947	2907	2655	2574	2518	2296

Figure 3. Kaplan-Meier curves of major adverse cardiac events for the nonreduced and reduced HDL subgroups in male and female patients. HDL = high-density lipoprotein; MACE = major adverse cardiac events.

Table 2
Adjusted comparisons between the nonreduced and reduced HDL groups in males and females

Outcome	Adjusted hazard ratio (95% confidence interval)	p value
Males		
Death	0.98 (0.61-1.56)	0.93
Myocardial infarction	0.89 (0.60-1.30)	0.54
Target vessel revascularization	1.37 (1.05-1.79)	0.02
Target lesion revascularization	1.36 (1.05-1.78)	0.02
Major adverse cardiac events	1.11 (0.90-1.37)	0.32
Females		
Death	1.01 (0.53-1.96)	0.96
Myocardial infarction	0.97 (0.59-1.61)	0.90
Target vessel revascularization	0.84 (0.55-1.27)	0.40
Target lesion revascularization	0.83 (0.55-1.26)	0.39
Major adverse cardiac events	0.85 (0.62-1.16)	0.31

have been unable to provide significant cardiovascular benefit.[5,6] This may be related to different anti-inflammatory and antioxidant capacity of the HDL molecule in the context of stable CAD and acute coronary syndrome.[11,12] In addition, protective actions of HDL may be attenuated in the presence of potent statin therapy.[13,14]

Low HDL has been shown to be an independent predictor of mortality and in-stent restenosis after PCI.[15–17] A post hoc analysis of the COURAGE trial, during which approximately 50% of enrolled patients underwent PCI, reported an inverse relation between HDL levels and the risk of death or MI.[18] Furthermore, an observational study indicated that high HDL during the first 3 months after PCI (on a background of normal low-density lipoprotein due to proper statin therapy), correlated with significantly lower MACE driven by lower TVR.[19] Nonetheless, contemporary evidence in the era of intense combination pharmacological therapy and modern coronary stents is scarce and sex-specific analyses are lacking. Epidemiological studies have suggested that both sexes may generally benefit from higher HDL levels[20] and the limited data from PCI patients report comparable impact in males and females.[15,19] Females are known to have higher baseline HDL than males (a higher cut-off point is widely adopted), but the clinical implications of nonreduced versus reduced HDL level are unclear.

We opted to implement guideline-directed HDL-level cutoffs utilized in daily clinical practice instead of population-driven quartiles as other trials have done. Our results appear concordant with previous evidence supporting a weakened relation between HDL and cardiovascular outcomes in patients who underwent PCI.[19] Even though an association between very low HDL and adverse cardiovascular events cannot be excluded based on the present analysis, we only found a nonsignificant difference in MACE, driven by borderline differences in TVR, which disappeared after adjusting for potential cofounders.

Our data showed that females with nonreduced HDL had similar outcomes to those with reduced HDL. Interestingly, males with nonreduced HDL had favorable 1-year outcomes compared with those with reduced HDL in terms of TVR even after adjustment. It is well known that females who underwent PCI constitute an entirely different population compared with males with respect to presentation, risk factors, and outcome measures.[21] As also evident in the present analysis women tend to present later in life with a higher burden of co-morbidities.[22] Moreover, their response to guideline recommended medications like aspirin and statins differs, potentially impacting the gravity of different cardiovascular risk factors.[23,24] The paucity of data regarding the sex-specific impact of HDL levels in patients with established CAD and PCI highlights the need for additional research efforts. The different baseline clinical and genetic profile as well as the different HDL cut-off point of the 2 sex subgroups could be affecting presented outcomes.

This study has several limitations. Stemming from a single-center prospective registry, our results may not be generalized to all patients who underwent PCI. In our dataset, only one baseline HDL measurement was recorded; this implies measurement bias and does not account for variation of HDL during the follow-up period. Although all patients are expected to be on statin therapy following PCI, we have no information regarding nonadherence or use of high intensity statin therapy. In addition, we have not assessed whether treatment intensity bias may exist by patient sex. Finally, despite adjusting for multiple covariates, we cannot exclude the possibility for residual unmeasured confounders including ethanol use, physical activity, and lifestyle modification. Hence, the results of this study should be considered hypothesis generating.

In conclusion, the prevalence of reduced HDL appeared high in this large PCI patient population. Rates of MACE were rather similar in HDL subgroups. Nonreduced baseline HDL was associated with borderline lower 1-year MACE, mostly driven by significantly lower TVR rate in male patients who underwent PCI; the latter should be further investigated.

Authors' Contributions

Anastasios Roumeliotis: Conceptualization, Methodology, Writing - Original Draft, Visualization; Bimmer Claessen: Conceptualization, Methodology, Writing - Review & Editing; George Dangas: Methodology, Investigation, Writing - Review & Editing, Supervision; Rebecca Torguson: Methodology, Writing - Review & Editing; Samantha Sartori: Software, Validation, Formal analysis, Data Curation; Adam Reisman: Writing - Original Draft, Visualization; Davide Cao: Methodology, Writing - Review & Editing; Rishi Chandiramani: Methodology, Writing - Review & Editing; Johny Nicolas: Methodology, Writing - Review & Editing; Ridhima Goel: Methodology, Writing - Review & Editing; Mauro Chiarito: Methodology, Writing - Review & Editing; Madhav Sharma: Conceptualization, Data Curation, Writing - Review & Editing; Dhrubajyoti Bandyopadhyay: Conceptualization, Writing - Review & Editing; Usman Baber: Investigation, Data Curation, Writing - Review & Editing; Joseph Sweeny: Investigation, Writing - Review & Editing; Nitin Barman: Investigation, Writing - Review & Editing; Samin Sharma: Investigation, Writing - Review & Editing; Annapoorna Kini: Investigation, Writing - Review & Editing; Roxana Mehran: Investigation,

Methodology, Data Curation, Writing - Review & Editing, Supervision.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.048.

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