Comparison of Hospitalization Trends and Outcomes in Acute Myocardial Infarction Patients With Versus Without Opioid Use Disorder

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Discrepancies in medical care are well known to adversely affect patients with opioid abuse disorders (OUD), including management and outcomes of acute myocardial infarction (AMI) in patients with OUD. We used the National Inpatient Sample was queried from January 2006 to September 2015 to identify all patients ≥18 years admitted with a primary diagnosis of AMI (weighted N = 13,030; unweighted N = 2,670) and concomitant OUD. Patients using other nonopiate illicit drugs were excluded. Propensity matching (1:1) yielded 2,253 well-matched pairs in which intergroup comparison of invasive revascularization strategies and cardiac outcomes were performed. The prevalence of OUD patients with AMI over the last decade has doubled, from 163 (2006) to 326 cases (2015) per 100,000 admissions for AMI. The OUD group underwent less cardiac catheterization (63.2% vs 72.2%; p <0.001), percutaneous coronary intervention (37.0% vs 48.5%; p <0.001) and drug-eluting stent placement (32.3% vs 19.5%; p <0.001) compared with non-OUD. No differences in in-hospital mortality/cardiogenic shock were noted. Among subgroup of ST-elevation myocardial infarction patients (26.2% of overall cohort), the OUD patients were less likely to receive percutaneous coronary intervention (67.9% vs 75.5%; p = 0.002), drug-eluting stent (31.4% vs 47.9%; p <0.001) with a significantly higher mortality (7.4% vs 4.3%), and cardiogenic shock (11.7% vs 7.9%). No differences in the frequency of coronary bypass grafting were noted in AMI or its subgroups. In conclusion, OUD patients presenting with AMI receive less invasive treatment compared with those without OUD. OUD patients presenting with ST-elevation myocardial infarction have worse in-hospital outcomes with increased mortality and cardiogenic shock. **(Am J Cardiol 2021;145:18−24)**

Prevalence of opioid abuse continues to rise in the United States (US), with opioid overdose-related deaths rising by 371% from 1999 to 2016.[1] Patients suffering from opioid use disorders (OUD) also suffer from cardiovascular disorders due to direct drug toxicity and as well as socioeconomic barriers in management of these disorders.[2−4] Impact of chronic opioid use on acute myocardial infarction (AMI) outcomes has not been well studied, as these patients have typically been excluded from all major clinical trials. We hypothesized that with the significant increase in OUD over the last decade, there would have been a significant increase in the number of patients with AMI and OUD. We further hypothesize that OUD has a considerable impact on the in-hospital management and treatment strategies in patients with AMI. We aimed to study the hospitalization trends, clinical characteristics, management strategies, and outcomes in patients with OUD who are admitted with AMI in the United States.

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See page 23 for disclosure information.

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Methods

Data were obtained from the National Inpatient Sample maintained by the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project. Briefly, this is a nationally representative database containing deidentified inpatient encounter level information. The National Inpatient Sample database was used to ascertain temporal trends, patient demographics, clinical characteristics, and inpatient outcomes during index hospitalization.[5] We selected all patients ≥18 years of age using International Classification of Diseases, 9th Edition (ICD-9) primary diagnosis codes for AMI, including both non-ST elevation and ST-elevation myocardial infarction (NSTEMI and STEMI). We then proceeded to identify patients with OUD using ICD 9 code as has been done in previous studies.[6] We excluded records with concomitant nonopioid substance abuse (cannabis, hallucinogens, barbiturates, cocaine, ampheramins, and antidepressants), as well as those with missing mortality and age. Due to the significant difference in baseline characteristics, we performed 1:1 propensity matching of the OUD patients with non-OUD

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patients. We matched the groups on basis of baseline demographics, socioeconomic status, and co-morbidities. The standardized mean difference was <10% for all variables (Supplementary Figure 1) suggesting a robust match.

The primary outcome of interest was all-cause in-hospital mortality at index hospitalization. Secondary outcomes of interest included cardiac arrest, cardiogenic shock, acute kidney injury (AKI), and AKI requiring hemodialysis. Treatment strategies for management of the AMI including cardiac catheterization, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) were studied for index hospitalization. Definitions and ICD-9-CM codes for these outcomes have been used in previous studies[7] and are listed in the Supplementary Table S2. As therapeutic approaches drastically differ according to the subtype of AMI, we performed subgroup analysis of the STEMI and NSTEMI groups.

Weighted data using Healthcare Cost and Utilization Project recommended complex survey design were used for all analyses to account for clustering and stratified sampling. Categorical and continuous variables were reported as percentages and mean ± standard error, respectively. In-hospital mortality was modeled into a multivariate logistic regression model adjusting for demographics, co-morbidities, complications, and treatment characteristics and reported as adjusted odds ratios and 95% confidence intervals. All data extraction and analyses were performed using SPSS (Version 22.0., Armonk, NY). Two-sided p value <0.05 was used for statistical significance.

Results

A total of 5,517,248 patients were admitted for AMI between 2006 and 2015 and of these 13,030 (0.2%; unweighted N = 2,670) had OUD (Supplementary Figure 2). Over this decade, there was a consistent and significant trend in the numbers of patients with OUD as a percentage of all AMI admissions, from 163 cases to 326 cases per 100,000 admissions (Figure 1).

Significant differences in baseline demographics between the OUD and non-OUD patients (Table 1) were present. OUD patients were significantly younger and fewer were women. There was a significantly higher percentage of minority populations (Blacks and Hispanics) in the OUD group. Although the mean Elixhauser comorbidity score was lower in the OUD group (with lower rates of diabetes, chronic kidney disease, and peripheral artery disease), several other co-morbidities were more common such as alcohol abuse, smoking and chronic pulmonary disease. A history of previous MI was more common in OUD group, but the history of prior coronary revascularization (PCI/CABG) was significantly lower. Significantly more OUD users were on Medicaid or were self-pay and more often presented to urban teaching hospitals. In terms of geographic spread across the United States, north-east and west regions had higher proportions of OUD patients in their AMI population.

Out of unweighted sample of 2,670 OUD patients, we were able to match 2,253 (84.3%) OUD patients. Mean age for the cohort was 56.9 years, with no difference in baseline cardiovascular risk factors, previous history of myocardial infarctions/revascularizations between matched groups (Table 2*)*:. Cardiogenic shock was only present in 4.9%. Out of total OUD patients, STEMI and NSTEMI patients were 26.2% and 73.8%, respectively.

There was no difference in the incidence of cardiogenic shock or in-hospital mortality between groups, though the OUD group had a higher incidence of cardiac arrest and AKI (Table 3). In the overall cohort, cardiac catheterization and PCI rates were significantly lower in the OUD group with lower rates of implantation of a drug-eluting stent (DES; Figure 2). No differences in rates of CABG were noted between the 2 groups (p = 0.95).

Subgroup analysis according to the presentation of NSTEMI or STEMI was done and demonstrated noteworthy differences (Table 4). Similar to the overall cohort, NSTEMI patients with OUD had a lower rate of cardiac catheterization compared with non-OUD group. PCI was

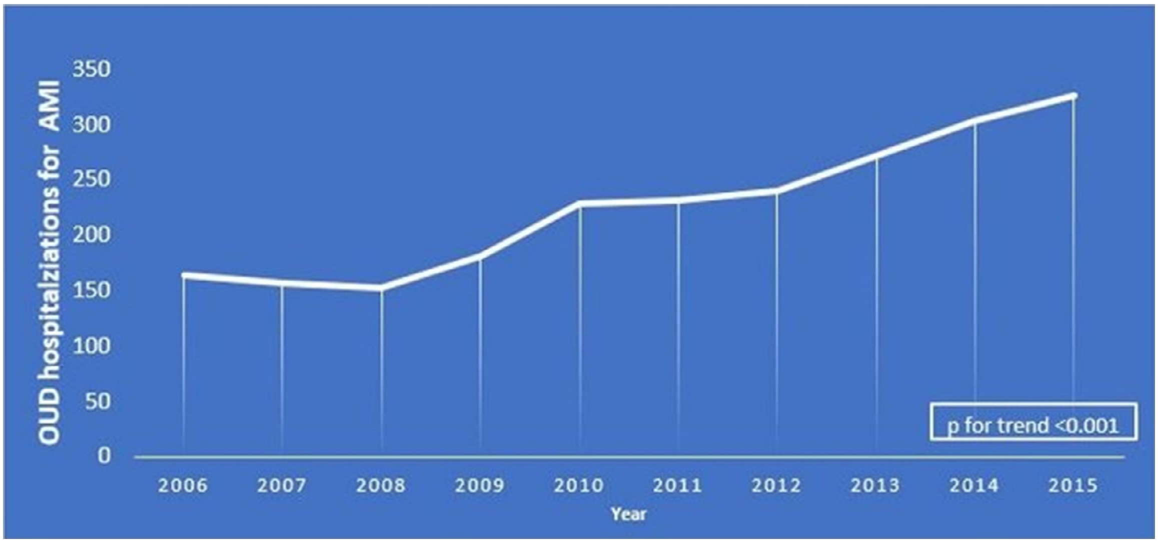

Figure 1. Temporal trend of OUD patients per 100,000 cases of ACS from 2006 to 2015 from the national inpatient database. AMI = acute myocardial infarction; OUD = opioid use disorder.

Table 1
Baseline characteristics of unmatched patients admitted for acute myocardial infarction according to opioid use disorder status

Variable	Opioid use disorder		p value
	No (N = 5,504,218)	Yes (N = 13,030)	
Age in years (±SE)	67.7 (±0.006)	56.6 (±0.1)	<0.001
Women	39.5%	35.8%	<0.001
White	76.6%	65.7%	<0.001
Black	9.6%	18.8%	<0.001
Hispanics	7.5%	10.0%	<0.001
Asian or Pacific Islander	2.4%	1.0%	<0.001
Native American	0.6%	0.5%	<0.001
Other	3.3%	4.0%	<0.001
Elixhauser co-morbidities			
0	9.8%	0.0%	<0.001
1-3	65.3%	43.7%	<0.001
>3	24.9%	56.3%	<0.001
Alcohol abuse	2.6%	14.3%	<0.001
Acquired immune deficiency syndrome	0.1%	1.7%	<0.001
Congestive heart failure	0.6%	0.9%	<0.001
Chronic obstructive pulmonary disease	20.7%	34.5%	<0.001
Diabetes mellitus	28.9%	22.4%	<0.001
Chronic kidney disease	15.0%	11.3%	<0.001
Peripheral vascular disease	11.5%	10.4%	<0.001
Hypertension	68.6%	65.5%	<0.001
Smoking	35.7%	61.1%	<0.001
Cardiac history			
Prior coronary artery bypass grafting	7.7%	5.5%	<0.001
Prior myocardial infarction	10.8%	11.6%	0.005
Prior percutaneous intervention	7.7%	5.5%	<0.001
Bed size of hospital			
Small	11.0%	12.1%	<0.001
Medium	24.9%	26.6%	<0.001
Large	64.1%	61.2%	<0.001
Location/teaching status of hospital			
Rural	9.8%	5.7%	<0.001
Urban nonteaching	40.2%	35.3%	<0.001
Urban teaching	50.0%	59.0%	<0.001
Hospital geographic region			
Northeast	19.4%	28.3%	<0.001
Midwest	23.3%	18.4%	<0.001
South	39.5%	30.8%	<0.001
West	17.8%	22.5%	<0.001
Primary expected Payer			
Medicare	57.5%	40.3%	<0.001
Medicaid	6.0%	27.3%	<0.001
Private insurance	27.7%	18.3%	<0.001
Self-pay	5.6%	9.4%	<0.001
No charge	0.6%	1.4%	<0.001
Other	2.7%	3.3%	<0.001

also less frequent in the OUD group and OUD patients were less likely to receive DES placement. However, in STEMI patients catheterization rates were similar between groups, though PCI was still performed less frequently in the OUD group and the use of DES was less frequent as well. No differences in CABG rates were seen in the groups.

STEMI patients with OUD had overall worse outcomes with higher in-hospital mortality, higher rates of cardiac arrest, and cardiogenic shock as well as AKI. In NSTEMI patients was no difference in in-hospital mortality or cardiogenic shock between OUD and non-OUD groups, but risk for cardiac arrest and AKI was still higher in the OUD patients. In terms of mechanical circulatory support, the IABP use was lower in both NSTEMI and STEMI patients with cardiogenic shock and OUD (Table S1).

Discussion

With the current ongoing epidemic of OUD in the United States, the interaction of OUD and AMI is a significant health issue. This study provides important new information regarding the trends in AMI in OUD patients, demographics and clinical characteristics of these patients and management strategies and outcomes at a nationwide

Table 2
Baseline characteristics of propensity matched patients admitted for acute myocardial infarction according to opioid use disorder status

Variable	Opioid use disorder		p value
	No (N = 2,253)	Yes (N = 2,253)	
Age (years)	56.9(13.4)	56.9(11.4)	1.0
Women	36%	36.5%	0.687
White	72.3%	67.5%	
Black	12.0%	18.7%	
Hispanic	8.0%	9.3%	
Asian	2.6%	1.0%	
Native American	0.8%	0.5%	
Type of acute myocardial infarction			
ST-elevation myocardial infarction	34.2%	26.2%	<0.001
Non-ST elevation myocardial infarction	65.8%	73.8%	<0.001
Median household income (percentile)			
0th-25th	35.6%	37.8%	0.13
26th-50th	26.5%	24.5%	0.10
51st-75th	21.4%	21.3%	0.94
76th-100th	16.4%	16.4%	0.96
Primary expected payer			0.21
Medicare	41.2%	41.4%	
Medicaid	13.4%	26.3%	
Private insurance	35.4%	18.2%	
Self-pay	8.3%	9.6%	
No charge	0.4%	1.5%	
Other	1.4%	3.1%	
Co-morbidities			
Acquired immune deficiency syndrome	0.2%	1.1%	<0.001
Congestive heart failure	0.7%	0.9%	0.503
Chronic pulmonary disease	34.9%	34.3%	0.661
Depression	15.7%	17.2%	0.172
Diabetes mellitus	21.4%	22.5%	0.350
Hypertension	65.1%	66.0%	0.490
Obesity	15.1%	14.2%	0.424
Valvular heart disease	0.2%	0.2%	0.739
Current smoking	64.7%	62.9%	0.204
Alcohol abuse	4.0%	14.3%	<0.001
Drug abuse	0.1%	100%	<0.001
Dyslipidemia	39.4%	40.0%	0.648
Hypothyroidism	8.0%	7.4%	0.468
Liver disease	1.8%	9.1%	<0.001
Renal failure	14.1%	15.8%	0.095
Cardiac history			
Known coronary artery disease	69.5%	68.8%	0.60
Prior coronary artery bypass grafting	5.8%	5.9%	0.899
Prior myocardial infarction	12.5%	12.4%	0.892
Prior percutaneous coronary intervention	5.8%	5.9%	0.899
Family history of coronary artery disease	12.2%	6.9%	<0.001

level. The main study findings are (1) there are significant differences in demographic and baseline clinical co-morbidities in OUD patients with AMI compared with non-OUD patients, (2) OUD patients undergo less cardiac catheterization and PCI and have a significantly less usage of DES, and (3) OUD patients with STEMI have significantly worse in-hospital mortality and other cardiovascular outcomes.

The significant trend of increasing admissions for AMI in OUD patients reflects the nationwide surge in opioid cases in the last 2 decades, mostly due to prescription misuse and use of synthetic opioids.[8,9] Our findings are also consistent with 2 recent studies that showed a significant increase in the number of OUD patients who underwent cardiac surgery in the United States over the last decade.[6,10] OUD patients were younger and predominantly men, which is reflective of the burden of opioid use in young male population especially between 25 and 44 years of age.[11] Geographically, these patients are predominantly from the north-east and the west USA regions, which are highly affected regions with opioid pandemic.[12,13] OUD patients had a significantly higher rates of accompanying addictions (smoking and alcohol abuse) as noted in other studies.[14−16] Peripheral artery disease, hypertension, previous coronary revascularization, and chronic kidney disease were less prevalent in these patients, probably due to younger age.

Table 3
Comparison of in-hospital outcomes in patients admitted with acute myocardial infarction according to opioid use disorder

Outcomes	Opioid use disorder		Odds ratio (95% CI)*	p value
	No (N = 2,253)	Yes (N = 2,253)		
In-hospital mortality	3.3%	4.2%	1.26 (0.92-1.72)	0.13
Cardiogenic shock	4.4 %	5.5%	1.25 (0.95-1.64)	0.09
Cardiac arrest	2.8%	4.7%	1.73(1.26-2.37)	<0.001
Acute kidney Injury	10.4%	17.4%	1.81 (1.52-2.15)	<0.001
Acute kidney Injury needing hemodialysis	0.4%	0.7%	1.50 (0.67-3.3)	0.31

* Propensity matched for age, sex, race, chronic heart failure, chronic lung disease, depression, diabetes, hypertension, obesity, valve disorders, smoking, dyslipidemia, known coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, and prior coronary bypass grafting.

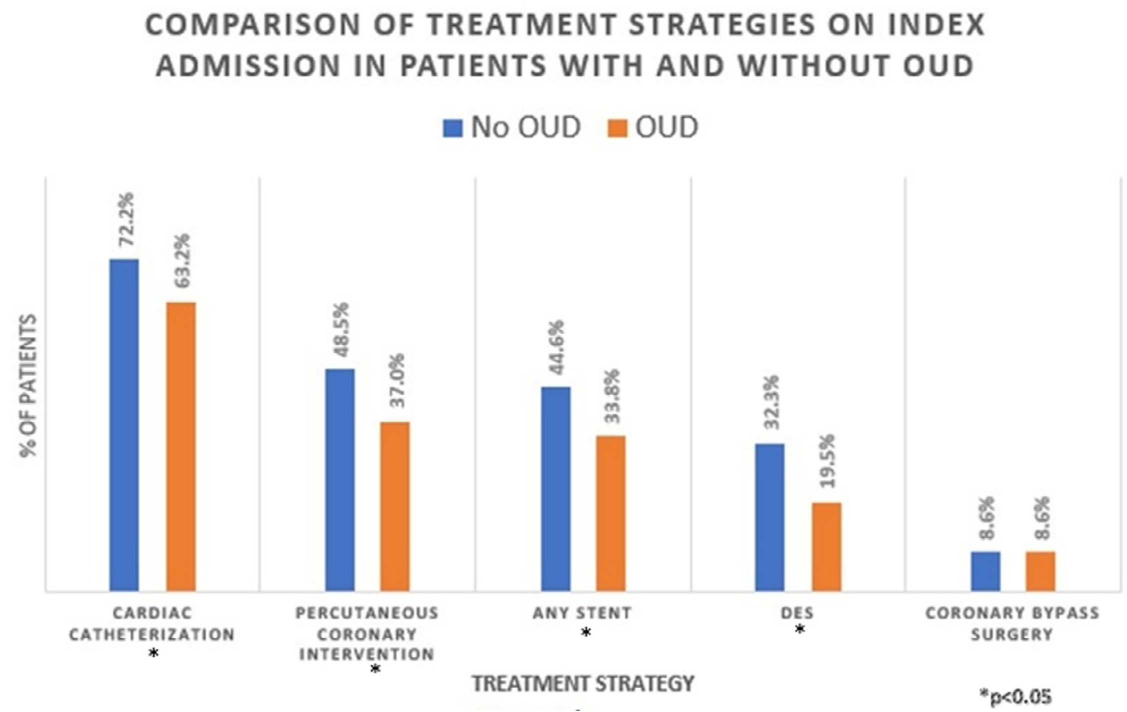

Figure 2. Comparison of treatment strategies in AMI patients with and without OUD. AMI = acute myocardial infarction; DES = drug-eluting stent; OUD = opioid use disorder.

Table 4
Comparison of outcomes and management of acute myocardial infarction for opioid use disorder patients

	Outcomes					
	Non-ST elevation of myocardial infarction patients			ST-elevation of myocardial infarction patients		
	OUD			OUD		
	No (N = 1,482)	Yes (N = 1,607)	p value	No (N = 771)	Yes (N = 592)	p value
Died	2.8%	3.0%	0.77	4.3%	7.4%	0.01
Cardiogenic shock	2.6%	3.3%	0.25	7.9%	11.7%	0.02
Cardiac arrest	1.8%	3.0%	0.02	4.8%	9.8%	<0.001
Acute kidney injury	12.3%	18.8%	<0.001	6.7%	13.7%	<0.001
Acute kidney injury needing hemodialysis	0.4%	0.5%	0.57	0.5%	1.0%	0.28
	Treatment strategy					
Cardiac catheterization	66.3%	57.1%	<0.001	83.5%	80.4%	0.13
Percutaneous coronary intervention	34.5%	25.9%	<0.001	75.5%	67.9%	0.002
Any stent	32.0%	23.8%	<0.001	68.9%	61.8%	0.007
Drug-eluting stent	24.0%	15.2%	<0.001	47.9%	31.4%	<0.001
Coronary bypass grafting	10.1%	8.8%	0.22	5.8%	7.9%	0.12

OUD = opioid use disorder.

There are multiple probable reasons that the OUD patients had a significantly lower utilization of invasive treatments. These include, concern about noncompliance with medications (especially antiplatelet agents) and lower suspicion of atherothrombotic coronary process in these younger group of patients. Interestingly, in patients with time-sensitive clinical presentation, like STEMI, no difference in cardiac catheterization rates were observed. This argues against an physician bias. Another interesting observation was the lower use of percutabeous intervention in OUD group that did undergo angiography. This was true even for patients with STEMI. Some possible (somewhat speculative) reasons for this finding could be that OUD patients had a later presentation (outside the window of benefit) or a higher incidence of small vessel occlusion. Though we excluded patients with concomitant other illicit drug use, coronary vasospasm may also be possible underlying mechanism for no intervention in some patients with OUD and STEMI.

Our current research on in-hospital outcomes in AMI in OUD patients is among the first reports on this topic and thus not much data are available for comparisons. The findings of significantly higher mortality, cardiogenic shock, cardiac arrest, and AKI in STEMI in OUD patients (even after matching for multiple variables) are concerning and identify OUD patients with STEMI as an exceptionally high-risk group. The findings in NSTEMI group were less striking with a higher risk of cardiac arrest and AKI but not of death or cardiogenic shock. The impact of OUD on CAD and its outcomes has not been studied in any systematic manner. Previous studies of acute coronary syndrome patients have been mainly focused on the effects of intravenous administration of morphine to opioid naïve patients with AMI.[17,18] They demonstrated reduced platelet inhibition, posited to be due to reduced blood concentration of P2Y12 inhibitors in a dose and time-dependent manner.[9,19] The clinical impact of this was not clear with multiple retrospective studies drawing conflicting conclusions.[17,20–22] A recently published post hoc analysis of the EARLY ACS trial of AMI patients did show an adverse effect of intravenous morphine on cardiovascular outcomes in patients who received clopidogrel pretreatment versus those who received a P2Y12 inhibitor in the catheterization laboratory.[23] The higher mortality in STEMI patients with OUD in our study may have in part resulted from the interaction of opioid with antiplatelet therapy, though the etiology is likely multifactorial including the possibility of a delayed presentation or less frequent use of PCI.

Our study has several limitations. There may be inaccuracies in coding of co-morbidities as well as procedures. A diagnosis of OUD does not indicate if the opioid use is current or remote. It also does not help identify the frequency and extent of opioid use. Although we excluded all other concomitant substance abuse (except alcohol and tobacco) some patients may still have been included due to coding errors in the database. No information is available in the database on several pertinent clinical variables such as time from symptom onset to presentation, cardiac enzymes levels, medication use, or coronary anatomy. These variables can have a significant impact on outcomes and even though we did rigorous propensity matching, these and other variables could not be accounted for completely.

In conclusion, patients with OUD presenting with AMI are younger, more are non-Caucasian and have a different cardiovascular risk profile than those without OUD. In a well-matched cohort, OUD patients underwent less invasive cardiac procedures including PCI and less frequent use of DES. OUD patients with more severe presentation such as cardiogenic shock also had less utilization of aggressive therapy such as mechanical circulatory devices. OUD patients with STEMI had higher mortality, cardiogenic shock, cardiac arrest, and AKI compared with non-OUD patients. The study identifies OUD as a strong adverse prognosticator in the setting of an AMI and the study findings prompt a further systematic study of factors resulting in these findings.

Authors' Contribution

Sagar Ranka: Conceptualization, Methodology, Formal analysis, Writing-Original draft preparation; Tarun Dalia: Writing-Original draft preparation, Conceptualization; Prakash Acharya: Formal analysis, Validation, Data Curation; Siva Sagar Taduru: Formal analysis, Resources, Methodology, Suveenkrishna Pothuru: Conceptualization, Writing-Review & Editing; Uzair Mahmood: Resources, Visualization; Brianna Stack: Writing-Review & Editing; Zubair Shah: Supervision, Writing-Review & Editing; Kamal Gupta: Conceptualization, Methodology, Writing-Review & Editing, Supervision.

Disclosures

None of the authors listed have any conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.077.

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