Frequency of Cardiovascular Events and In-hospital Mortality With Opioid Overdose Hospitalizations

Rajkumar Doshi, MD, MPH[a],[*], Monil Majmundar, MD[b], Tikal Kansara, MD[b], Rupak Desai, MBBS[c], Jay Shah, MD[d], Ashish Kumar, MBBS[e], and Krunalkumar Patel, MD[f]

The United States is in the kernel of cataclysmic opioid misuse epidemic with over 33,000 deaths per year from both prescription and illegal opioids use. One of the most common pernicious effects of opioids is on the cardiovascular system. The purpose of this analysis was to determine the incidence of opioid overdose associated cardiovascular events and its impact on short-term outcomes. This was a retrospective, observational study which utilized data from the National Inpatient Sample from January 2005 to September 2015 using *International Classifications of Disease, Ninth Revision, Clinical Modification* diagnosis codes to identify patients with opioid overdose and associated cardiovascular outcomes. Cardiovascular events were mainly divided into the following 3 parts: Ischemic Events (ischemic stroke and myocardial infarction), acute heart failure, and arrhythmias. The primary outcome of this study was incidence of any cardiovascular event. This study analyzed a total of 430,459 patients hospitalized with opioid overdose, out of which 36,837 (8.6%) had at least 1 cardiovascular event. In all the opioid overdose hospitalizations, 13,979 (3.2%) developed ischemic events, 3,074 (0.7%) developed acute heart failure, and 22,444 (5.2%) developed arrhythmia. Opioid overdose patients with new-onset cardiovascular events had higher odds for in-hospital mortality (odds ratio 4.55; 95% confidence interval 4.11 to 5.04, p <0.001) as compared to patients without cardiovascular events in the multivariable-adjusted model. This study group also demonstrated longer length of stay and higher cost of hospitalization associated with opioid overdose and associated cardiovascular outcome. In conclusion, opioid overdose is associated with higher rates of cardiovascular events, particularly ischemic events and cardiac arrhythmias. These adverse events eventually lead to higher mortality rates and more resource utilization.   © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:1528−1533)

Deaths owing to opioid overdose have increased nearly sixfold since 1999.[1] From the period 1999 to 2017, prescriptions for opioid analgesics in the United States grew by 700%,[2] and nearly 400,000 people died from an opiate overdose, including prescription and illicit opioids use.[3] Overdoses involving opioids killed 47,600 people in 2017[3] and on average, 130 Americans die every day from an opioid overdose.[1] It also imparts a significant economic burden of $78.5 billion per year.[4] Few small studies have investigated adverse effects of opioid abuse or chronic opioid use on cardiovascular system[5] mainly atrial fibrillation,[6] QTc prolongation, consequent torsade de pointes[7,8] and coronary artery disease/myocardial infarction.[9,10] The incidence of these cardiovascular events frequently requires extensive workup which further amplifies economic burden.[6,11] There is limited evidence demonstrating the association between opioid overdose and cardiovascular events. Opioids are used vitally in alleviating control chronic pain, and hence, the knowledge of its interaction with the cardiovascular system is indispensable for a clinician. In a previously published study demonstrating the burden of arrhythmias associated with opioid overdose hospitalization, we reported the incidence of atrial fibrillation of approximately 4.1% after admission with opioid overdose.[12] In this study, we demonstrated the association between opioid overdose and incidences of ischemic events, heart failure, and arrhythmias that developed during the hospital stay.

Methods

This study utilized data from the National Inpatient Sample (NIS). The details of the NIS database have been published earlier.[13] In brief, the NIS was developed by the Healthcare Cost and Utilization Project and is sponsored by the Agency for Healthcare Research and Quality. It comprises 20% sample of all United States hospitalizations and represents more than 95% of the US population. In the present study, we utilized data from January 2005 to September 2015. After September 2015, use of International Classifications of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was not possible due to the use of ICD-10-CM codes after this period. The design of the study was changed during the period which is described earlier.[14] To account

[a]Department of Internal Medicine, University of Nevada Reno School of Medicine, Reno, Nevada; [b]Department of Internal Medicine, Metropolitan Hospital Center, New York Medical College, New York, New York; [c]Division of Cardiology, Atlanta VA Medical Center, Decatur, Georgia; [d]Department of Internal Medicine, Mercy St Vincent Medical Center, Toledo, Ohio; [e]Department of Critical Care Medicine, St John's Medical College Hospital, Bangalore, India; and [f]Department of Cardiology, North Shore University Hospital, Manhasset, New York. Manuscript received June 20, 2019; revised manuscript received and accepted July 30, 2019.

See page 1533 for disclosure information.

*Corresponding author: University of Nevada Reno School of Medicine, Department of Internal Medicine, 1155 Mill St, W11, Reno Nevada, United States 89502.

E-mail address: raj20490@gmail.com (R. Doshi).

for this change, a new set of weights called "trend weights" were developed and utilized for the data from 2005 to 2011. As the NIS is a publicly available deidentified national dataset, these analyses were exempt from the institutional review board of the University of Nevada Reno School of Medicine.

This was a retrospective, observational study using the nation's largest, publicly available database from January 2005 to September 2015. A total of 439,928 hospitalizations were identified using ICD-9-CM diagnosis codes in the primary diagnostic column. Then, hospitalizations below 18 years of age were excluded from the analysis (n = 9,438). A total of 430,459 hospitalizations were included in the final analysis. Out of which, 34,342 hospitalizations had at least 1 cardiovascular outcome, and 396,117 hospitalizations did not have any cardiovascular outcomes during admission. Out of these 34,342 hospitalizations, 13,979 had ischemic events, 3,074 had acute heart failure, and 22,444 had an arrhythmia. Ischemic events comprised of ischemic stroke (n = 3,153) or acute coronary syndrome (ST-segment elevated myocardial infarction [n = 297] or non-ST-segment elevated myocardial infarction [n = 10,963]). Acute heart failure comprised of both heart failure with reduced ejection fraction (n = 1,603) and heart failure with preserved ejection fraction (n = 1,471). Arrhythmia comprised of atrial fibrillation (n = 17,695), atrial flutter (n = 1,548), ventricular fibrillation (n = 1,150), ventricular flutter (n = 5), ventricular tachycardia (n = 3,102), and supraventricular tachycardia (n = 657) (Supplementary Figure 1).

The Elixhauser co-morbidities derived from ICD-9-CM codes and diagnosis-related groups and previously published ICD-9-CM codes were used to identify individual co-morbidities for our study. A previously utilized strategy was used to identify patients with opioid overdose in this study.[12,15] We utilized 965.00 (opium), 965.02 (methadone), and 965.09 (other opiates and narcotics) codes to identify our study population. Additionally, previously utilized ICD-9-CM and strategy were utilized to identify study outcomes which were ischemic events, acute heart failure, and arrhythmias.[16–20] (Ischemic stroke 433.x1, 434.x1, 436, 437.1, acute myocardial infarction 410.xx, acute systolic heart Failure 428.21, 428.23, acute diastolic heart failure 428.31, 428.33, atrial fibrillation 427.31, atrial flutter 427.32, atrioventricular block 426.0, 426.1, ventricular tachycardia 427.1, ventricular fibrillation 427.41, supraventricular tachycardia 427.0).

All analyses were performed using SAS 9.4 which accounted for the complex survey, stratification, and clustering per recommendation (SAS Institute Inc., Cary, North Carolina).[21] We have attached a checklist in the Supplementary Figure 2 following all recommendations from the NIS.[22] National estimates were generated using discharge weights provided by the sponsor. All tests were 2-sided, and the level of significance was set at a p value of less than 0.05. Continuous variables were expressed as mean (± standard deviations [SD]) or median (interquartile range), according to variable distribution. Categorical variables were expressed as percentages. Intergroup and intragroup comparisons of continuous variables were analyzed using the Wilcoxon rank-sum test, and categorical variables were analyzed using the Chi-square test. The total charges for each hospital stay were converted to cost estimates

using the group average all-payer in-hospital cost and charge information from the detailed reports by hospitals to the Centers for Medicare and Medicaid Services. Final cost was calculated by multiplying the total cost with the cost-to-charge ratio provided by the sponsor. This study also included multivariate logistic regression analysis. For this analysis, we utilized age, sex, race, insurance status, income, co-morbidities, and all the hospital level variables in the model to analyze in-hospital mortality.

Results

The present study included a total of 430,459 adults, hospitalization with opioid overdose. Of these, 36,837 (8.6%)

Table 1

Demographics and baseline characteristics of patients with and without cardiovascular event admitted with opioid overdose

Variable name	Cardiovascular event		p Value
	No (N = 393,622)	Yes (N = 36,837)	
Age (Years)	46.4 ± 16.0	55.9 ± 18.1	<0.001
Males	195,067 (49.6%)	20,229 (54.9%)	<0.001
Females	198,430 (50.4%)	16,608 (45.1%)	
White	277,659 (70.6%)	27,354 (74.3%)	<0.001
Black	29,776 (7.6%)	2,639 (7.2%)	
Others	86,147 (21.9%)	6,834 (18.6%)	
Hypertension	136,883 (34.8%)	18,013 (48.9%)	<0.001
Diabetes mellitus	50,065 (12.7%)	6,186 (16.8%)	<0.001
Obesity	33,064 (8.4%)	4,466 (12.1%)	<0.001
Chronic pulmonary disease	92,985 (23.6%)	11,954 (32.5%)	<0.001
Chronic renal disease	23,768 (6%)	5,135 (13.9%)	<0.001
Chronic liver disease	23,497 (6%)	2,001 (5.4%)	<0.001
Alcohol abuse	65,392 (16.6%)	5,246 (14.2%)	<0.001
Smoker	139,957 (35.6%)	8,611 (23.4%)	<0.001
Dyslipidemia	43,502 (11.1%)	5,796 (15.7%)	<0.001
Primary payer			
Medicare/Medicaid	222,604 (56.6%)	24,989 (67.9%)	<0.001
Private insurance	84,565 (21.5%)	6,352 (17.3%)	
Other	86,276 (21.9%)	5,491 (14.9%)	
Median household income (In percentile)			
0-25th	121,323 (31.9%)	11,001 (30.6%)	<0.001
26-50th	103,043 (27.1%)	9,758 (27.1%)	
51-75th	89,562 (23.6%)	8,654 (24.1%)	
76-100th	66,393 (17.5%)	6,578 (8.3%)	
Admission type			
Elective	9,190 (2.3%)	805 (2.2%)	0.06
Emergent/Urgent	383,546 (97.7%)	35,988 (97.8%)	
Hospital region			
Northeast	72,784 (18.5%)	6,800 (18.5%)	<0.001
Midwest	88,664 (22.5%)	7,860 (21.3%)	
South	148,129 (37.6%)	13,851 (37.6%)	
West	84,045 (21.4%)	8,326 (22.6%)	
Hospital teaching status			
Rural	50,635 (12.9%)	3,814 (10.4%)	<0.001
Urban, nonteaching	165,121 (42.2%)	15,206 (41.6%)	
Teaching	175,622 (44.9%)	17,563 (48%)	
Hospital bed-size			
Small	55,038 (14.1%)	4,778 (13.1%)	<0.001
Medium	109,690 (28%)	10,166 (27.8%)	
Large	226,651 (57.9%)	21,640 (59.1%)	

Obesity is defined as body mass index above 30 kg/m². Elevated hypertension and dyslipidemia were defined using international classification of diseases ninth revision codes and were already present in the database.

hospitalizations had at least 1 cardiovascular event during the same hospitalization. The hospitalized patients with cardiovascular event were older compared with those without any cardiovascular event (56 vs 46 years, p = <0.001). Prevalence of males and females with opioid overdose was equal; however, the study yielded higher cardiovascular events in males compared with females. Majority of the hospitalizations were Caucasians in both groups. Overall, the group with cardiovascular events manifested a greater burden of co-morbidities. Hypertension (48.9%), chronic pulmonary disease (32.5%), smokers (23.4%), and diabetes mellitus (16.8%) were observed to be highest in hospitalized patients with cardiovascular events. There was a greater prevalence of hospitalizations with Medicare/Medicaid insurance as their primary payer. The same group also generated the highest cardiovascular events (67.9%) compared with other insurances. Hospitalizations with lower household income were noted to have higher cardiovascular events. Near 98% hospitalizations were emergent/urgent. South American had the highest prevalence of opioid overdose hospitalizations. Hospitalizations for opioid overdose were highest in the teaching and large bed hospitals (Table 1). There were 13,979 hospitalizations with ischemic events (3.2%), 3,074 with acute heart failure (0.7%) and 22,444 with arrhythmias (5.2%). Out of 13,979 ischemic events, 11,260 had acute coronary syndrome (ST-segment elevated myocardial infarction or non-ST-segment elevated myocardial infarction) (2.6%) and 3,153 has ischemic stroke (0.7%). A frequency of each outcome per 1,000 opioid overdose hospitalizations is shown in Figure 1. In opioid overdose hospitalizations, the arrhythmia group had the highest mean age. Females with opioid overdose experienced higher prevalence of heart failure (54% vs 46%, p = <0.001). Caucasians were pre-eminent in all the groups. Table 2 demonstrated other characteristics. Overall incidence of any cardiovascular events and each separate event spiraled high during the study period (Supplementary Figure 3).

Crude in-hospital mortality was approximately 4 times higher in the group with cardiovascular events as compared with no cardiovascular events (9.1% vs 2.2%, p = <0.001). After adjusting for variables, the group of opioid overdose hospitalizations with cardiovascular events yielded higher odds of mortality (Odds Ratio [OD] 4.55, confidence interval [CI] 3.11 to 5.04, p = <0.001). Length of stay (4 vs 2 days, p = <0.001) and cost of care ($10,406 vs $5,140, p = <0.001) were almost double in hospitalizations with cardiovascular events. Crude mortality increased nearly fivefold in the group with ischemic events compared with no cardiovascular events (11.5% vs 2.2%, p = <0.001). Similarly, adjusted in-hospital mortality was higher in ischemic group (OD 4.49, CI 3.90 to 5.17, p = <0.001). Length of stay (5 vs 2 days, p = <0.001) and cost of care ($15,786 vs $5,140, p = <0.001) increased approximately threefold in ischemic group. Likewise, higher crude (5.3% vs 2.2%, p = <0.001) and adjusted mortality (OD 1.89, CI 1.30 to 2.75, p = <0.001) was observed in the heart failure group when compared with no cardiovascular events. The length of stay (5 vs 2 days, p = <0.001) and cost of care ($14,438 vs $5,140, p = <0.001) almost tripled as well. Finally, the group of arrhythmias exhibited higher crude (9.8% vs 2.2%, p = <0.001) and adjusted mortality (OD 4.12, CI 3.65 to 4.66, p = <0.001) compared with no cardiovascular events. Their length of stay (3 vs 2 days,
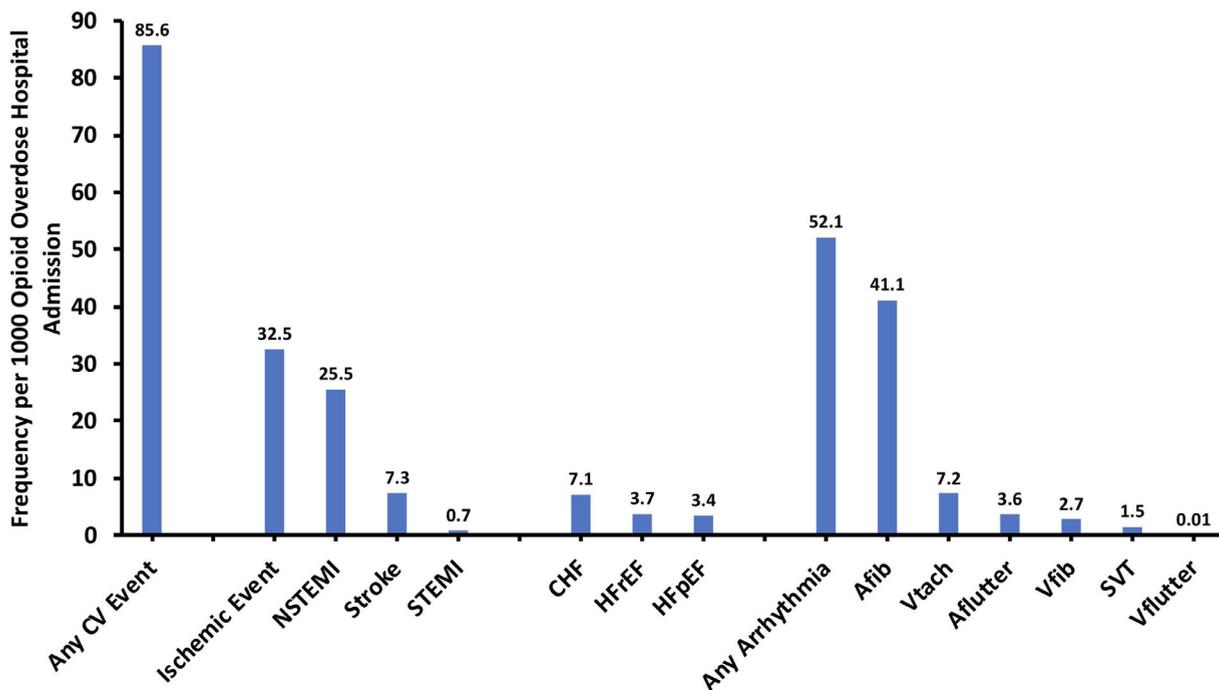

Figure 1. Frequency of cardiovascular event per 1,000 hospital admissions with opioid overdose. CV = Cardiovascular; NSTEMI = Non-ST segment elevated myocardial infarction; STEMI = ST-segment elevated myocardial infarction; CHF = congestive heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; Afib = atrial fibrillation; Vtach = ventricular tachycardia; Aflutter = atrial flutter; VFib = ventricular fibrillation; SVT = supraventricular tachycardia; VFlutter = ventricular flutter.

Table 2
Demographics and baseline characteristics of patients admitted with opioid overdose: Stratified by the type of cardiovascular outcome

Variable name	Ischemic event (N = 13,979)	Acute heart failure (N = 3,074)	Arrhythmia (N = 22,444)
Age (Years)	50.3 ± 16.6	58.6 ± 16.4	59.3 ± 18.4
Males	7,645 (54.7%)	1,413 (46%)	12,646 (56.3%)
Females	6,334 (45.3%)	1,661 (54%)	9,798 (43.7%)
White	10,103 (72.3%)	2,225 (72.4%)	17,058 (76%)
Black	1,019 (7.3%)	311 (10.1%)	1,495 (6.7%)
Others	2,853 (20.4%)	539 (17.5%)	3,886 (17.3%)
Hypertension	5,877 (42%)	1,675 (54.5%)	11,863 (52.9%)
Diabetes mellitus	1,776 (12.7%)	659 (21.4%)	4,237 (18.9%)
Obesity	1,461 (10.5%)	741 (24.1%)	2,664 (11.9%)
Chronic pulmonary disease	3,708 (26.5%)	1,403 (45.7%)	7,759 (34.6%)
Chronic renal disease	1,432 (10.2%)	667 (21.7%)	3,473 (15.5%)
Chronic liver disease	811 (5.8%)	159 (5.2%)	1,184 (5.3%)
Alcohol abuse	2,108 (15.1%)	340 (11.1%)	3,155 (14.1%)
Smoker	3,200 (22.9%)	550 (17.9%)	5,281 (23.5%)
Dyslipidemia	1,703 (12.2%)	498 (16.2%)	3,958 (17.5%)
Primary payer			
Medicare/Medicaid	8,461 (60.5%)	2,410 (78.4%)	15,994 (71.3%)
Private Insurance	2,882 (20.6%)	357 (11.6%)	3,511 (15.7%)
Other	2,636 (18.9%)	308 (10%)	2,933 (13.1%)
Median household income (In percentile)			
0-25th	4,561 (33.5%)	1,012 (33.7%)	6,214 (28.3%)
26-50th	3,581 (26.3%)	858 (28.6%)	6,063 (27.6%)
51-75th	3,205 (23.5%)	708 (23.6%)	5,408 (24.6%)
76-100th	2,289 (16.8%)	424 (14.1%)	4,276 (19.5%)
Admission type			
Elective	286 (2%)	69 (2.2%)	530 (2.4%)
Emergent/Urgent	13,684 (98%)	3,006 (97.8%)	21,879 (97.6%)
Hospital region			
Northeast	2,680 (19.2%)	494 (16.1%)	4,064 (18.1%)
Midwest	2,862 (20.5%)	693 (22.6%)	4,874 (21.7%)
South	5,697 (40.8%)	1,198 (39%)	8,010 (35.7%)
West	2,739 (19.6%)	688 (22.4%)	5,496 (24.5%)
Hospital teaching status			
Rural	1,355 (9.8%)	377 (12.3%)	2,377 (10.7%)
Urban, nonteaching	5,692 (41%)	1,146 (37.4%)	9,330 (41.9%)
Teaching	6,833 (49.2%)	1,543 (50.3%)	10,585 (47.5%)
Hospital bed-size			
Small	1,705 (12.3%)	379 (12.4%)	3,014 (13.5%)
Medium	3,980 (28.7%)	805 (26.3%)	6,150 (27.6%)
Large	8,195 (59%)	1,882 (61.4%)	13,123 (58.9%)

p = <0.001) and cost of care ($8,119 vs $5,140, p = <0.001) were increased compared with other groups as well (Table 3). In the multivariate analysis, demographics such as age, male gender, and white race predicted cardiovascular events (Table 4). Additionally, obesity, chronic pulmonary disease, and chronic renal disease predicted cardiovascular events in patients admitted with opioid overdose (Supplementary Table 1).

Discussion

The present study documented that in patients with opioid overdose hospitalization, cardiovascular events were more common in elderly, male, and Caucasian patients. Most of the people belonged to low median household income, and Medicaid/Medicare was the primary payer. Opioid overdose hospitalizations were more common in the southern part of the United States as compared with other regions. Overall, the incidence of any cardiovascular event,

ischemic event, acute heart failure, and arrhythmia spiraled significantly high during the study period. Arrhythmias were the most common cardiovascular events followed by ischemic events. Atrial fibrillation was the most common arrhythmia associated with opioid overdose. Opioid overdose associated with cardiovascular events led to higher in-hospital mortality, length of stay, and cost burden as compared with those without cardiovascular events. In patients with opioid overdose hospitalization, older age, male sex, white race, obesity, chronic pulmonary, and renal disease were the positive predictor of any cardiovascular events. This study is the largest to date, demonstrating the association of opioid overdose hospital admission with cardiovascular events in the United States.

The 3 most common cardiovascular events discussed in this study were ischemic events, acute heart failure, and arrhythmias. Opioids have been associated with a decrease in cardiac function, causing bradycardia and vasodilation (especially when used with benzodiazepines).[5] Perhaps, the

Table 3
In-hospital outcomes associated with opioid overdose hospitalizations

Outcome			p Value
	Any cardiovascular event (N = 36,837)	*No cardiovascular event (N = 396,117)*	
In-hospital mortality[†]	3,361 (9.1%)	8,580 (2.2%)	<0.001
Adjusted mortality*	4.55 (4.11-5.04)		<0.001
Length of Stay (Median)	4 (2-8)	2 (1 − 4)	<0.001
Cost in $$ (Median)	10,406 (5,870-19,794)	5,140 (3,178 - 8,981)	<0.001
	Ischemic event (N = 13,979)	*No cardiovascular event (N = 396,117)*	
In-hospital mortality[†]	1,607 (11.5%)	8,580 (2.2%)	<0.001
Adjusted mortality*	4.49 (3.90-5.17)		<0.001
Length of Stay (Median)	5 (3-10)	2 (1 − 4)	<0.001
Cost (Median)	15,786 (9,098 - 27,243)	5,140 (3,178 - 8,981)	<0.001
	Heart failure (N = 3,074)	*No cardiovascular event (N = 396,117)*	
In-hospital mortality[†]	162 (5.3%)	8,580 (2.2%)	<0.001
Adjusted mortality*	1.89 (1.30-2.75)		<0.001
Length of Stay (Median)	5 (3 − 9)	2 (1 − 4)	<0.001
Cost (Median)	14,438 (7,737 − 24,742)	5,140 (3,178 - 8,981)	<0.001
	Arrhythmia (N = 22,444)	*No cardiovascular event (N = 396,117)*	
In-hospital mortality[†]	1,967 (9.8%)	8,580 (2.2%)	<0.001
Adjusted mortality*	4.12 (3.65-4.66)		<0.001
Length of Stay (Median)	3 (2 − 6)	2 (1 − 4)	<0.001
Cost (Median)	8,119 (4,911 − 14,900)	5,140 (3,178 − 8,981)	<0.001

* Adjusted for age, sex, race, insurance status, income, co-morbidities, and all the hospital level variables.
[†] Frequency missing = 644.

most common side effect of opioids is the prolongation of QT interval, which can lead to torsades de pointes.[23] As a result of this phenomenon, arrhythmias were the most common cardiovascular event and occurred in nearly more than half of patients with cardiovascular events. In all hospitalizations, 5.2% were attributable to some form of arrhythmia. Previous studies like the one by Cynthia Lee et al[24] had shown that morphine increases the risk of atrial fibrillation in breast cancer patients. In the study, 2.6% of hospitalizations were due to an acute coronary syndrome. A study by Zedler et al[25] showed that myocardial infarction was present in 3.4% patients with opioid toxicity. Previous studies have confirmed that with chronic opioid use, risk of myocardial infarction increases significantly.[5,9,26] Mechanism of opioid-induced myocardial infarction is multifactorial and may include increased myocardial oxygen demand, marked vasoconstriction of coronary arteries, acidosis, and direct toxic effects on coronary arteries.[27] Opioid overdose with cardiovascular events are associated with substantially higher in-hospital mortality which is explained by higher mortality rates of cardiovascular events itself. Additionally, the length of hospital stay, as well as the cost of hospitalization, were double than opioid abusers without cardiovascular events.

This study gives more insight into an ongoing humongous muddle of opioid overdose. The impact of adverse effects with opioid abuse and overdose is not just limited to the individual but also extend to his or her family, friends, and nationwide. Opioids overdose has significant effects on public health outcomes related to neuropsychiatric manifestations and cardiovascular effects like ischemic effects, heart failure, and arrhythmias, public safety hazards such as crime, violence, and drugged driving; and a tremendous economic burden associated with increased health care costs, lost productivity, and criminal justice costs. The present study gives a physician an alternative perspective to look at a patient with opioid overdose and consider it as a potential risk factor for the development of cardiovascular events during the hospitalization which leads to increased mortality, the burden of cost, and resource utilization. Early identification of cardiovascular events may help prevent excess mortality, morbidity, and associated financial burden.

There are a several limitations associated with this study as with any sizeable observational study using administrative claims data. As with any other retrospective study, we may have miscoding error as diagnosis were made based on administrative codes. We may have underreporting of co-morbid conditions.[13] However, administrative codes were found to be specific, especially for cardiovascular diagnosis and risk factors.[28] All the types of opioids do not have similarly cardiac side effects.[5] We do not have information on individual opioid drug and dosage which may limit interpretation to specific opioid medication. There is no information on concurrent use of other drugs such as benzodiazepine, cocaine which can increase the cardiovascular adverse effects and that can play as a confounding factor in the study.[29] We may have

Table 4
Positive predictors for cardiovascular event when hospitalized with opioid overdose

Variable	Odds ratio with confidence interval	p Value
Age (every 10 year)	1.39 (1.32-1.45)	<0.001
Males vs females	1.62 (1.54-1.71)	<0.001
White vs Black	1.33 (1.20-1.47)	<0.001
Obesity	1.28 (1.18-1.38)	<0.001
Chronic pulmonary disease	1.28 (1.21-1.35)	<0.001
Chronic renal disease	1.53 (1.42-1.66)	<0.001

overestimated cardiovascular events as using secondary diagnosis codes for identification of new-onset events is not always accurate. However, this idea has been utilized by multiple previous articles.[20,30] Finally, we do not have information on new onset QTc prolongation following opioid overdose which is thought to be one of the significant arrhythmias.

In conclusion, opioid overdose associated admission were most common in Southern America. Opioid overdose-related hospitalizations are associated with new cardiovascular events, especially arrhythmias and ischemic events. Additionally, cardiovascular events associated with opioid overdose spiraled significantly during the study period. The incidence of cardiovascular events led to increased mortality, length of stay, and eventually expanded the burden of the cost on the healthcare system. Timely recognition and prompt treatment of cardiovascular events may improve the in-hospital mortality in patients with opioid overdose.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.068.

1. Hedegaard H, Miniño AM, Warner M. Drug Overdose Deaths in the United States, 1999-2017. NCHS Data Brief, no 329. Hyattsville, MD: National Center for Health Statistics. https://www.cdc.gov/nchs/products/databriefs/db329.htm. Accessed on January 1, 2019.
2. Department of Justice Drug Enforcement Administration. Automation of reports and consolidated orders system (ARCOS) (http://www.deadiversion.usdoj.gov/arcos/index.html). Accessed on January 1, 2019.
3. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths - United States, 2013-2017. Morb Mortal Wkly Rep. https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm. Accessed on January 1, 2019.
4. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the United States, 2013. Med Care 2016;54:901–906.
5. Chen A, Ashburn MA. Cardiac effects of opioid therapy. Pain Med 2015;16(Suppl 1):S27–S31.
6. Qureshi WT, O'Neal WT, Khodneva Y, Judd S, Safford MM, Muntner P, Soliman EZ. Association between opioid use and atrial fibrillation: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. JAMA Intern Med 2015;175:1058–1060.
7. Xuan C, Wu N, Li Y, Sun X, Zhang Q, Ma H. Corrected QT interval prolongation during anesthetic induction for laryngeal mask airway insertion with or without cisatracurium. J Int Med Res 2018;46:1990–2000.
8. Afshari R, Maxwell S, Dawson A, Bateman DN. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. Clin Toxicol (Phila) 2005;43:255–259.
9. Li L, Setoguchi S, Cabral H, Jick S. Opioid use for noncancer pain and risk of myocardial infarction amongst adults. J Intern Med 2013;273:511–526.
10. Marmor M, Penn A, Widmer K, Levin RI, Maslansky R. Coronary artery disease and opioid use. Am J Cardiol 2004;93:1295–1297.
11. Reinhart M, Scarpati LM, Kirson NY, Patton C, Shak N, Erensen JG. The economic burden of abuse of prescription opioids: a systematic literature review from 2012 to 2017. Appl Health Econ Health Policy 2018;16:609–632.
12. Doshi R, Shah J, Desai R, Gullapalli N. Burden of arrhythmia in hospitalizations with opioid overdose. Int J Cardiol 2019;286:73–75.
13. Patel N, Kalra R, Doshi R, Bajaj NS, Arora G, Arora P. Trends and cost of heart transplantation and left ventricular assist devices: impact of proposed federal cuts. JACC Heart Fail 2018;6:424–432.
14. Khera R, Cram P, Lu X, Vyas A, Gerke A, Rosenthal GE, Horwitz PA, Girotra S. Trends in the use of percutaneous ventricular assist devices: analysis of national inpatient sample data, 2007 through 2012. JAMA Intern Med 2015;175:941–950.
15. Gaither JR, Leventhal JM, Ryan SA, Camenga DR. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. JAMA Pediatr 2016;170:1195–1201.
16. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. JAMA Cardiol 2017;2:181–187.
17. Goyal P, Almarzooq ZI, Horn EM, Karas MG, Sobol I, Swaminathan RV, Feldman DN, Minutello RM, Singh HS, Bergman GW, Wong SC, Kim LK. Characteristics of hospitalizations for heart failure with preserved ejection fraction. Am J Med 2016;129:635.e615-626.
18. Doshi R, Decter DH, Meraj P. Incidence of arrhythmias and impact of permanent pacemaker implantation in hospitalizations with transcatheter aortic valve replacement. Clin Cardiol 2018;41:640–645.
19. Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. JAMA 2011;306:2248–2254.
20. Kalra R, Patel N, Doshi R, Arora G, Arora P. Evaluation of the incidence of new-onset atrial fibrillation after aortic valve replacement. JAMA Intern Med 2019;8:1122–1130.
21. Khera R, Angraal S, Couch T, Welsh JW, Nallamothu BK, Girotra S, Chan PS, Krumholz HM. Adherence to methodological standards in research using the National Inpatient Sample. JAMA 2017;318:2011–2018.
22. Khera R, Krumholz HM. With great power comes great responsibility: big data research from the National Inpatient Sample. Circ Cardiovasc Qual Outcomes 2017;10.
23. Behzadi M, Joukar S, Beik A. Opioids and cardiac arrhythmia: a literature review. Med Princ Pract 2018;27:401–414.
24. Lee CW, Muo CH, Liang JA, Lin MC, Kao CH. Atrial fibrillation is associated with morphine treatment in female breast cancer patients: a retrospective population-based time-dependent cohort study. Medicine (Baltimore) 2016;95:e3102.
25. Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, Rajan P, Baser O, Murrelle L. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med 2014;15:1911–1929.
26. Carman WJ, Su S, Cook SF, Wurzelmann JI, McAfee A. Coronary heart disease outcomes among chronic opioid and cyclooxygenase-2 users compared with a general population cohort. Pharmacoepidemiol Drug Saf 2011;20:754–762.
27. Sztajzel J, Karpuz H, Rutishauser W. Heroin abuse and myocardial infarction. Int J Cardiol 1994;47:180–182.
28. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–485.
29. Hernandez I, He M, Brooks MM, Zhang Y. Exposure-response association between concurrent opioid and benzodiazepine use and risk of opioid-related overdose in medicare part d beneficiaries. JAMA Network Open 2018;1:e180919.
30. Gupta T, Goel K, Kolte D, Khera S, Villablanca PA, Aronow WS, Bortnick AE, Slovut DP, Taub CC, Kizer JR, Pyo RT, Abbott JD, Fonarow GC, Rihal CS, Garcia MJ, Bhatt DL. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. JACC Cardiovasc Interv 2017;10:2050–2060.