ORIGINAL RESEARCH

Outcomes of Patients with Opioid-Related Diagnoses in Acute Coronary Syndrome: a National Inpatient Sample-Based Analysis

Yeunjung Kim, MD, MPH[1], Justin M. Pacor, MD[2], Albert Do, MD, MPH[2], Joseph Brennan, MD[1], David A. Fiellin, MD[2,3], and E. Jennifer Edelman, MD, MHS[2,4]

[1]Division of Cardiovascular Medicine, Department of Medicine, Yale School of Medicine, New Haven, CT, USA; [2]Section of General Internal Medicine, Department of Medicine, Yale School of Medicine, New Haven, CT, USA; [3]Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA; [4]Department of Social and Behavioral Medicine, Yale School of Public Health, New Haven, CT, USA.

BACKGROUND: Acute coronary syndrome (ACS) and opioid use are both major causes of morbidity and mortality globally. Although epidemiological studies point to increased risk of ACS in opioid users, in-hospital management and outcomes are unknown for this population when presenting with ACS. We sought to determine whether there are differences for in-hospital outcomes and management of ACS for those with and without opioid-related diagnoses (ORD).

METHODS AND RESULTS: From the National Inpatient Sample database, we extracted patients hospitalized between 2012 and 2016 for ACS. The primary independent variable was ORD by International Classification of Diseases, 9th and 10th Revision, codes. The primary outcome was in-hospital mortality; secondary outcomes were cardiac arrest, receipt of angiogram, and percutaneous coronary intervention (PCI). Statistical comparisons were performed using χ^2 test and Student's *t* test. Multivariable logistic regression was performed to determine the independent association between ORD and outcomes of interest. Among the estimated 5.8 million admissions for ACS, the proportion of patients with ORD increased over the study period (p for trend < 0.01). Compared to patients without ORD presenting with ACS, patients with ORD were younger with fewer cardiovascular risk factors. Yet, in-hospital mortality was higher in patients with ORD presenting with ACS (AOR 1.36, 95% CI 1.26–1.48). Patients with ORD were more likely to experience in-hospital cardiac arrest (AOR 1.42, 95% CI 1.23–1.63) and less likely to undergo angiogram (AOR 0.42, 95% CI 0.38–0.45) or PCI (AOR 0.30, 95% CI 0.28–0.32).

CONCLUSION: Despite evidence of increased risk of mortality and cardiac arrest, patients with ORD admitted for ACS are less likely to receive ACS management.

KEY WORDS: Opioid-related diagnoses; Acute coronary syndrome; Cardiac arrest; Percutaneous Coronary intervention.

Abbreviations

ACS	Acute coronary syndrome
AMA	Against medical advice
AMI	Acute myocardial infarction
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
NSTEMI	Non-ST elevation myocardial infarction
ORD	Opioid-related diagnoses
PCI	Percutaneous coronary intervention
STEMI	ST elevation myocardial infarction
VT	Ventricular tachycardia

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INTRODUCTION

Globally, opioid use is associated with growing rates of morbidity and mortality.[1] With an estimated 130 Americans dying from opioid overdoses each day, it surpasses all other causes of preventable death.[1] In addition to overdose, patients who use opioids are at an increased risk for infectious diseases, including human immunodeficiency virus, hepatitis C virus, and endocarditis.[2,3] Opioid use may complicate the care of these conditions as patients may be less likely to engage in care, stay in care, and receive quality care.[4] This difference in care has been well described in the context of chronic disease management in the outpatient setting, and more recently in the context of endocarditis in the inpatient setting.[5]

To our knowledge, there are few studies on whether opioid-related diagnoses (ORD) impact the management and outcomes of acute coronary syndrome (ACS). Opioids have been implicated in the decreased absorption of antiplatelet therapy, which impacts outcomes in ACS.[6–12] Moreover, psychosocial and behavioral factors related to opioid use may lead to delay in recognition and timely intervention in ACS—both of which can be a challenge in a population that may delay seeking care and may face uneven delivery of care.[13–16]

The primary objectives of this study were (1) to examine temporal trends and correlates of patients admitted with ACS and ORD, (2) to determine whether in-hospital outcomes differed by presence of ORD, and (3) to compare the use of coronary angiography in the management of ACS. We

hypothesized that ORDs may increase the risk of in-hospital mortality among patients with ACS independent of differences in psychosocial and cardiovascular risk profiles and based on processes of clinical management.

METHODS

We analyzed the National Inpatient Sample (NIS) 2012–2016, developed and updated by the Agency for Healthcare Research and Quality (AHRQ). Discharge level data analysis was limited to 2012–2016 due to sampling methodology changes made by the AHRQ in 2012. This timeframe also captures the rise in opioid use reported by the Centers for Disease Control.[17] Discharge diagnoses (up to 30) were listed for each observation using International Classification of Disease-Ninth and Tenth Edition-Clinical Modification (ICD-9/10-CM). ICD-10-CM officially went into effect in October 2015. This study was exempt from Yale University institutional review board given use of publicly available, de-identified data.

Study Population

We included all adults (age ≥ 18) hospitalized with ACS, defined with ICD-9/10-CM codes (Fig. 1). ACS was defined by ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina using ICD-9/10-CM codes (online Table 1). Any discharge diagnosis code consistent with ACS was included in the study population. Based on existing literature, lack of coding precision, and a desire to assess exposure as an opioid class effect,[18] ORD was defined using ICD-9-CM codes consistent with opioid receipt for chronic pain and use among individuals with addiction. This includes codes for opioid use disorder, opium, opioid, synthetic narcotic, or heroin use, dependence, and poisoning (online Table 1). We then mapped these ICD-9-CM codes to relevant ICD-10 codes.

Study Variables

NIS provides demographic characteristics including age, sex, socioeconomic status (estimated by median household income of residents in the patients' ZIP code), and race. Comorbidities including diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease (CKD), history of coronary artery disease, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), atrial fibrillation, smoking, and obesity were abstracted using ICD-9/10-CM codes (online Table 1). In addition, hospital course (including ventricular tachycardia, cardiogenic shock, transfusions, respiratory failure, and sepsis) was determined using ICD-9/10-CM codes. Hospital disposition and length of stay were provided in the NIS dataset.

Outcomes of Interest

The primary outcome was in-hospital mortality as assessed using the NIS dataset. Secondary outcomes were in-hospital cardiac arrest and treatment with coronary angiogram with or without PCI, which are the standard of care for ACS.[19,20] ACS-related management was abstracted using the ICD 9/10-Procedure Coding System.[21,22]

Statistical Analysis

National admission trends were approximated using AHRQ weight trends. Both weighted and unweighted observations were obtained. Statistical evaluation was performed using the Rao-Scott chi-square test for weighted samples and Student's *t* test for continuous variables. Weighted values are provided by NIS to approximate the total number of hospital admissions and provide descriptive statistics of the population of interest.

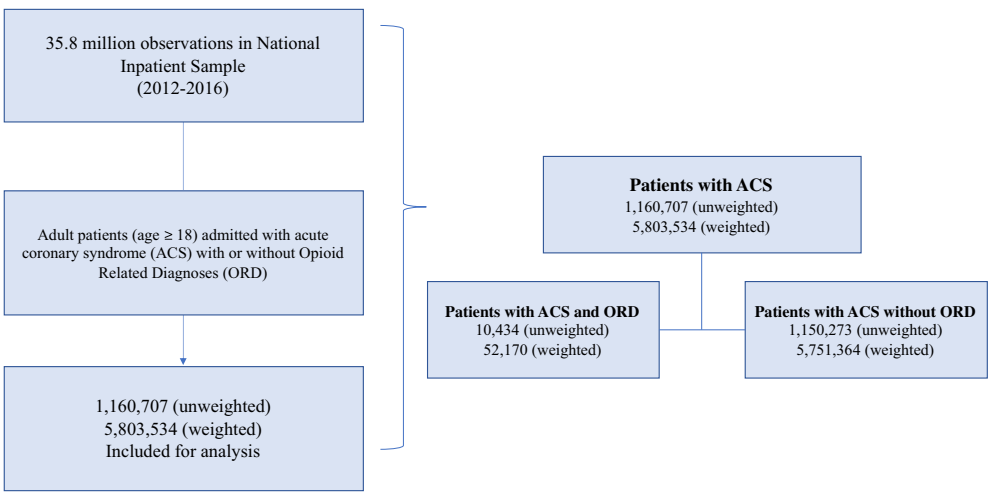

Figure 1 Flowchart of patient population. Schematic showing the extraction of hospitalizations from the National Inpatient Sample between 2012 and 2016. Adult patients with acute coronary syndrome with and without opioid-related diagnoses were enrolled using International Classification of Diseases, Ninth and Tenth Revision, codes. Of note, hospitalizations may represent the same patient if there were readmissions meeting the inclusion criteria.

The Cochran-Armitage trend test was used to determine the annual trend in concurrent ORD and ACS admissions between 2012 and 2016. Hospitalizations were stratified by age groups 18–39, 40–64, 65–74, 75–89, and ≥ 90 years old. Both univariate and multivariate analyses were performed using logistic regressions accounting for weights, hospital strata, and clusters. In-hospital mortality odds ratios (OR) were adjusted by age stratum, race, sex, hypertension, hyperlipidemia, diabetes, CKD, heart failure, STEMI, and PCI. This model was built based on cardiovascular risk factors associated with in-hospital mortality (online Table 8). Secondary outcomes were adjusted for covariates including age, sex, race, and socioeconomic status; CKD; STEMI; and respiratory failure. We used a two-tailed p value < 0.01 as statistically significant for purposes of sampling error given the size of the dataset. A regression model was used in order to understand how each chosen variable impacted the outcome, instead of a propensity score analysis which would attempt to rid outliers and adjust for variables included in the analysis.

Sensitivity analysis was performed to compare patients with strict ACS diagnosis (defined as principal discharge diagnosis of ACS) to a less stringent ACS diagnosis (defined as ACS in the top 3 discharge diagnosis codes). Primary and secondary outcomes were evaluated in the sensitivity analyses using both adjusted and unadjusted logistic regression models. Twenty-nine Elixhauser comorbidity classification variables were determined using a list of ICD-9/10 codes and added for further adjustments.[23] All statistical analyses were performed using the SAS 9.4 for Windows (Cary, NC), and figures were produced by GraphPad Prism version 8.0 for MacOS (San Diego, CA).

RESULTS

Study Population

Overall, there were 5.8 million admissions for ACS during this period, of which 0.9% of patients had comorbid ORD, totaling 52,170 admissions for ACS with an ORD between 2012 and 2016. The proportion of patients admitted with ACS who had comorbid ORD more than doubled from 2012 to 2016 (650 [0.6%] hospitalizations to 1569 [1.6%] hospitalizations per 100,000 ACS hospitalizations, p for trend < 0.01). The rise was greatest among 40–65-year-old patients. This same group, however, had the greatest decrease in hospitalizations for ACS alone (Fig. 2A, B). In the study population, unstable angina (10% vs 18%, p < 0.01) and STEMI (15% vs 21%, p < 0.01) were less common in patients with ORD, while NSTEMI (75% vs 62%, p < 0.01) was more common in patients with ORD.

Correlates of ORD Among Those Admitted with ACS

The patients with ORD compared to those with non-ORD were younger (57 vs 67 years, p < 0.01), more likely to be black (16% vs 12%, p < 0.01), and of lower socioeconomic status (38% vs 31%, p < 0.01) (Table 1). Patients with ORD had lower rates of diabetes (30% vs 40%, p < 0.01), hypertension (61% vs 74%, p < 0.01), hyperlipidemia (36% vs 60%, p < 0.01), history of coronary artery disease (52% vs 77%, p < 0.01), and atrial fibrillation (14% vs 22%, p < 0.01), but were more likely to be current smokers (43% vs 36%, p < 0.01) and use other substances (online Table 6). Patients with ORD were

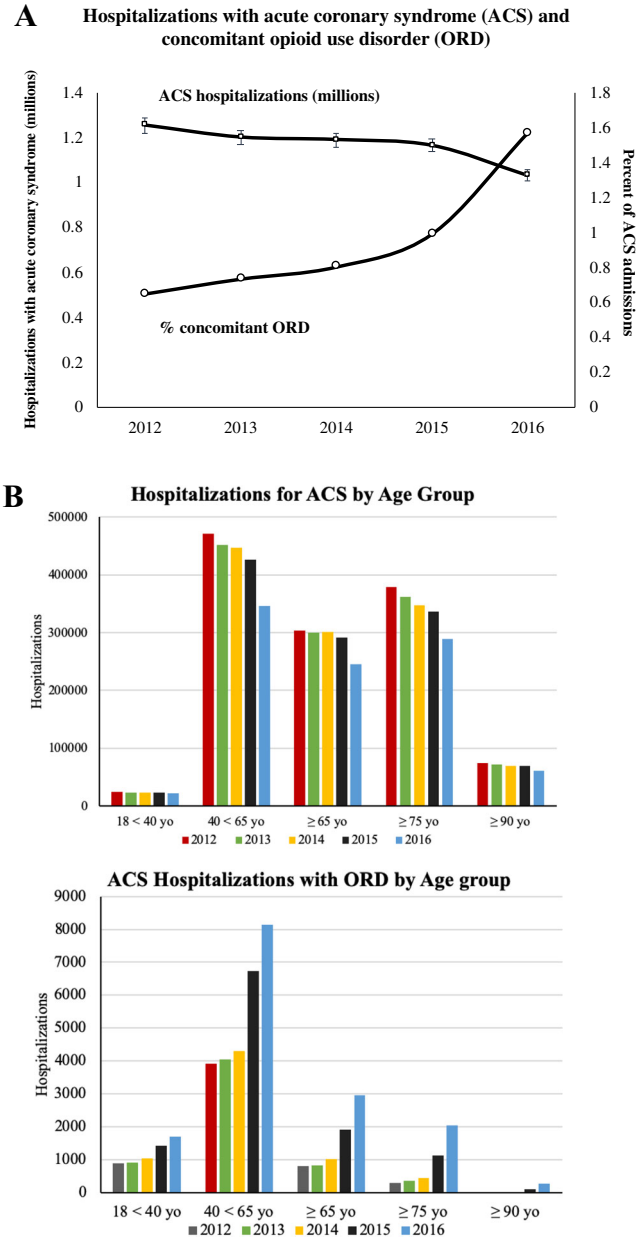

Figure 2 A Hospitalizations for acute coronary syndrome and the rise of concomitant opioid-related diagnoses. A Number of ACS hospitalizations between 2012 and 2016 and percent (%) with concomitant ORD. B Stratification by age groups showing a decline in annual admissions for ACS, while there is an increase in ACS with ORD in all age groups. The younger age group (40 < 65 years old) had both the greatest decline in ACS and the largest increase in ACS with ORD. Error bars represent standard error. *Abbreviations*: ACS, acute coronary syndrome; ORD, opioid-related diagnoses.

Table 1 Patient Characteristics in ACS by ORD (*N* = 5,803,534)

	ORD (*N* = 52,170)	No ORD (*N* = 5,751,364)	*p* value*
Demographic data			
Age (SE)	57 (15)	67 (15)	< 0.01
Female	44.3%	43.0%	0.10
Race			< 0.01
White	71%	74%	
Black	16%	12%	
Hispanic	8%	8%	
Asian	1%	3%	
SE status			< 0.01
25th percentile	38%	31%	
26th–50th percentile	26%	27%	
51th–75th percentile	22%	23%	
76th–100th percentile	14%	19%	
Comorbidities			
Diabetes	29.6%	40.1%	< 0.01
Hypertension	60.8%	73.7%	< 0.01
Hyperlipidemia	35.7%	60.0%	< 0.01
Chronic kidney disease	18.9%	25.9%	< 0.01
Coronary artery disease	51.8%	76.5%	< 0.01
Obesity	13.9%	15.8%	< 0.01
Smoking	43.1%	35.9%	< 0.01
COPD	30.2%	20.3%	< 0.01
CHF	26.7%	32.5%	< 0.01
Atrial fibrillation	13.5%	22.0%	< 0.01

ACS acute coronary syndrome, ORD opioid-related disorders, SE socioeconomic, COPD chronic obstructive pulmonary disease, CHF congestive heart failure
**All p values calculated with Student's t test for continuous variables and chi-square test with Rao-Scott correction for categorical variables*

also more likely to have COPD (30% vs 20%, $p < 0.01$) than those without ORD.

Hospital Course Among Those With and Without ORD

Cardiogenic shock (5.8% vs 5.2%, $p = 0.02$) was greater in patients with ORD while prevalence of ventricular tachycardia was similar between groups (5.2% vs 5.4%, $p = 0.20$) (Table 2). Respiratory failure (35% vs 15%, $p < 0.01$) and sepsis (19% vs 9%, $p < 0.01$) were more frequent in patients with ORD. In addition, patients with ORD had longer hospital stays (6.9 days vs 5.4 days, $p < 0.01$), had more frequent discharges to a nursing facility (19% vs 17%, $p < 0.01$), and were more likely to leave against medical advice (4% vs 1%, $p < 0.01$) (Table 2).

Primary and Secondary Outcomes

The in-hospital mortality rate was 6.5% overall; it was 7.6% among those with ORD and 6.5% among those without ORD (OR 1.19, 95% CI 1.11–1.28). After adjustment, in-hospital

Table 2 Hospital Course in ACS by ORD (*N* = 5,803,534)

	ORD (*N* = 52,170)	No ORD (*N* = 5,751,364)	*p* value*
Hospital events			
Angiogram	36.3%	53.7%	< 0.01
PCI	16.2%	33.4%	< 0.01
STEMI	15.1%	20.6%	< 0.01
CV shock	5.8%	5.2%	0.02
Cardiac arrest	5.7%	3.6%	< 0.01
VT	5.2%	5.4%	0.20
Transfusions	2.8%	1.6%	< 0.01
Respiratory failure	35.4%	15.1%	< 0.01
Sepsis	18.6%	9.1%	< 0.01
Length of stay (SD)	6.9 (8.6)	5.4 (6.8)	< 0.01
In-hospital mortality	7.6%	6.5%	< 0.01
Disposition			< 0.01
Routine discharge	51%	56%	
Short-term hospital	6%	7%	
Nursing facility	19%	17%	
Home health services	12%	13%	
AMA	7.6%	1.1%	

SD standard deviation, ACS acute coronary syndrome, ORD opioid-related disorders, PCI percutaneous coronary intervention, STEMI ST elevation myocardial infarction, CV shock cardiogenic shock, VT ventricular tachycardia, AMA against medical advice
**All p values calculated with Student's t test for continuous variables and chi-square test with Rao-Scott correction for categorical variables*

mortality was greater in patients with ORD (AOR 1.36, 95% CI 1.26–1.48). For secondary outcomes, cardiac arrest (5.7% vs 3.6%) was more common in ORD with unadjusted (OR 1.60, 95% CI 1.48–1.75) and adjusted (AOR 1.42, 95% CI 1.23–1.63) analyses. Coronary angiography (36% vs 54%) was less common in patients with ORD in unadjusted (OR 0.48, 95% CI 0.46–0.50) and adjusted (AOR 0.33, 95% CI 0.31–0.35) analyses. Similarly, PCI was less common in ORD with unadjusted (OR 0.38, 95% CI 0.37–0.41) and adjusted (AOR 0.30, 95% CI 0.28–0.32) analyses (Table 3). This trend was consistent in all age groups except in patients older than 90 years of age (online Table 4).

Subgroup analyses performed for in-hospital mortality revealed greatest odds of in-hospital mortality in younger patients [in ages between 18 and 39 (AOR 2.83, 95% CI 2.30–3.48) and ages between 40 and 64 (AORD 1.39, 95% CI 1.24–1.55)]. In-hospital mortality was greatest in STEMI (AOR 1.49, 95% CI 1.26–1.76) than NSTEMI (AOR 1.19, 95% CI 1.08–1.31). White (AOR 1.41, 95% CI 1.28–1.54) and Hispanic (AOR 1.49, 95% CI 1.14–1.96) patients had greater odds of in-hospital mortality with ORD. ORD was associated with increased in-hospital mortality in all socioeconomic quartiles (Table 4).

Table 4 Subgroup Analysis for In-Hospital Mortality (Patient Characteristics)

Subgroup (% total study population)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age stratum		
18–39 (5%)	7.72 (6.47–9.22)	2.83 (2.32–3.45)
40–64 (37%)	1.93 (1.75–2.14)	1.39 (1.25–1.54)
65–74 (24%)	1.01 (0.83–1.23)	0.82 (0.67–1.00)
75–89 (29%)	0.83 (0.67–1.03)	0.78 (0.62–0.97)
≥ 90 (6%)	0.80 (0.47–1.37)	0.91 (0.53–1.57)
Race		
White (74%)	1.19 (1.09–1.30)	1.41 (1.28–1.54)
Black (12%)	1.07 (0.87–1.31)	1.17 (0.95–1.44)
Hispanic (8%)	1.36 (1.06–1.75)	1.49 (1.15–1.94)
Asian (3%)	1.02 (0.50–2.11)	1.00 (0.47–2.10)
Socioeconomic status		
25% percentile (31%)	1.18 (1.04–1.33)	1.36 (1.20–1.55)
26–50% percentile (27%)	1.13 (0.98–1.31)	1.30 (1.11–1.52)
51–75% percentile (23%)	1.29 (1.11–1.51)	1.43 (1.21–1.68)
≥ 76% percentile (19%)	1.20 (0.99–1.45)	1.36 (1.10–1.67)
Acute coronary syndrome		
STEMI (21%)	1.38 (1.20–1.60)	1.49 (1.28–1.74)
NSTEMI (62%)	1.09 (1.00–1.19)	1.19 (1.08–1.30)
Unstable angina (18%)	0.91 (0.52–1.62)	1.20 (0.68–2.14)

ACS acute coronary syndrome, ORD opioid-related diagnoses, CHF congestive heart failure, SE socioeconomic status, CKD chronic kidney disease, STEMI ST elevation myocardial infarction, PCI percutaneous coronary intervention
**Adjusted for age, race, sex, hypertension, hyperlipidemia, diabetes, CKD, CHF, STEMI, and PCI*

Sensitivity Analysis

In the sensitivity analysis, the study population was derived based on the position of the ICD diagnosis code. In the strict ACS population, where ACS was the principal discharge diagnosis, 100% of the population had ACS as the principal diagnosis as expected while 95% of the less stringently (first 3 diagnosis codes) defined ACS population had a principal hospital diagnosis of ACS (online Table 3). This is in contrast to 92% of cases having ACS as the principal diagnosis in the main study population where ACS was within any discharge diagnoses. When stratified by ORD status, the ORD group had more diagnoses of sepsis, respiratory failure, and substance abuse/poisoning reaching up to 45% (online Table 3). The sensitivity analysis of the primary outcome (in-hospital mortality) revealed that the ORD group had increased in-hospital mortality in the strict ACS population, but this did not meet statistical significance. However, as ACS became the second or third discharge diagnosis, ORD status was significantly associated with increased in-hospital mortality (Fig. 3). When stratified by age, ORD was associated with increased in-hospital mortality regardless of the location of ACS diagnosis (as the discharge diagnosis) when the patient was less than 65 years old (Table 5). Similarly, the ORD group consistently had lower odds of coronary angiography based on age (patients < 75 years old) (Table 5). There was no significant difference in the findings of increased in-hospital mortality with ORD after adjusting for possible confounders such as

Table 3 In-Hospital Mortality and Cardiac Arrest in ACS with ORD

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Primary outcomes		
In-hospital mortality*	1.19 (1.11–1.28)	1.36 (1.26–1.48)
Secondary outcomes		
Cardiac arrest*	1.61 (1.46–1.77)	1.39 (1.28–1.52)
Angiogram†	0.49 (0.47–0.52)	0.43 (0.40–0.45)
PCI†	0.39 (0.36–0.41)	0.36 (0.34–0.39)

ACS acute coronary syndrome, ORD opioid-related diagnoses, CHF congestive heart failure, SE socioeconomic status, CKD chronic kidney disease, STEMI ST elevation myocardial infarction, PCI percutaneous coronary intervention
**Primary outcome and cardiac arrest adjusted for age, race, sex, hypertension, hyperlipidemia, diabetes, CKD, CHF, STEMI, and PCI*
†Procedure utilization adjusted for age, race, SE, CKD, STEMI, and respiratory failure

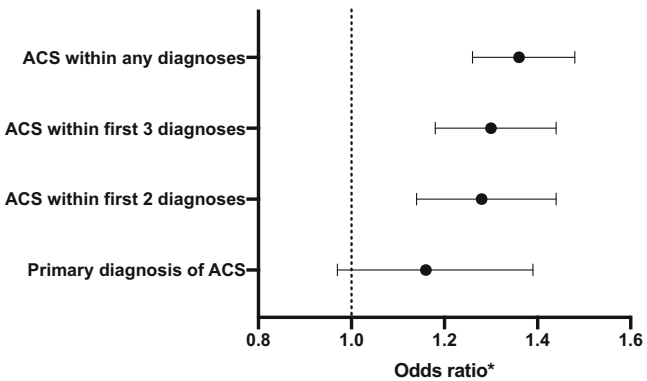

Figure 3 Impact of ORD on in-hospital mortality: sensitivity analysis by restricting study population based on location of ACS diagnosis in the list of discharge diagnoses. *Adjusted for age, race, sex, hypertension, hyperlipidemia, diabetes, chronic kidney disease, congestive heart failure, ST elevation myocardial infarction, and percutaneous coronary intervention.

Table 5 Impact of ORD on In-Hospital Mortality and Coronary Angiography, Stratified by Age: Sensitivity Analysis by Restricting Study Population Based on Location of ACS Diagnosis in the List of Discharge Diagnoses

	Odds ratio (95% CI)				
	Age (18–39)	Age (40–64)	Age (65–74)	Age (75–89)	Age (≥ 90)
In-hospital mortality*					
Principal diagnosis (ACS)	2.30 (1.13–4.69)	1.32 (1.05–1.68)	0.73 (0.46–1.15)	0.93 (0.60–1.44)	1.13 (0.45–2.83)
ACS within 2 diagnoses	3.43 (2.39–4.91)	1.39 (1.18–1.64)	0.82 (0.60–1.11)	0.89 (0.65–1.21)	0.90 (0.44–1.82)
ACS within 3 diagnoses	3.16 (2.41–4.13)	1.39 (1.22–1.59)	0.81 (0.63–1.04)	0.83 (0.64–1.08)	0.97 (0.55–1.70)
ACS within any diagnoses	2.83 (2.32–3.45)	1.39 (1.25–1.54)	0.82 (0.67–1.00)	0.78 (0.62–0.97)	0.91 (0.53–1.57)
Coronary angiography†					
Principal diagnosis (ACS)	0.72 (0.53–0.98)	0.57 (0.51–0.63)	0.71 (0.59–0.85)	0.89 (0.72–1.11)	1.51 (0.76–3.02)
ACS within 2 diagnoses	0.43 (0.35–0.53)	0.45 (0.42–0.49)	0.56 (0.49–0.64)	0.64 (0.54–0.76)	1.14 (0.68–1.92)
ACS within 3 diagnoses	0.35 (0.29–0.42)	0.44 (0.41–0.47)	0.55 (0.48–0.62)	0.57 (0.49–0.67)	0.93 (0.57–1.50)
ACS within any diagnoses	0.32 (0.27–0.38)	0.43 (0.40–0.46)	0.54 (0.48–0.61)	0.54 (0.47–0.63)	1.27 (0.78–1.94)

CI confidence interval
**Adjusted for race, sex, hypertension, hyperlipidemia, diabetes, chronic kidney disease, congestive heart failure, ST elevation myocardial infarction, and percutaneous coronary intervention*
†Adjusted for socioeconomic status, race, chronic kidney disease, respiratory failure, sepsis, peripheral vascular disease, metastatic cancer, solid tumors, and ST elevation myocardial infarction

tumors and metastatic cancer determined from Elixhauser comorbidity variables (online Table 4). After exclusion of AMA hospitalizations, the ORD group remained less likely to undergo angiogram in unadjusted (OR 0.50, 95% CI 0.48–0.53) and adjusted (AOR 0.44, 95% CI 0.41–0.46) analyses.

DISCUSSION

To our knowledge, this is the first study to compare the characteristics, outcomes, and management of patients with and without ORD admitted with ACS. Using data from a large national cohort, our study demonstrates that patients with ACS and comorbid ORD had an increased risk of in-hospital mortality despite a lower prevalence of traditional CVD risk factors including diabetes, hypertension, hyperlipidemia, and obesity. Furthermore, patients with ORD were less likely to undergo coronary angiogram and/or PCI perhaps leading to the differences in in-hospital outcomes, such as cardiac arrest and mortality. These findings are important and highlight a potential contributor of the premature mortality observed among patients with ORD.

Our study reveals that in-hospital mortality in ORD is seen specifically in younger patients (< 65 years old) presenting with STEMI (Table 4). Moreover, there is a greater prevalence of STEMI in this group compared to younger patients without ORD. As opposed to plaque rupture seen in atherosclerotic coronary artery disease, young patients tend to experience plaque erosion, spontaneous coronary artery dissection, vasospasm, and thromboembolic events during acute myocardial infarction (AMI).[19,20] This is corroborated by the lower prevalence of CVD risk factors in young patients and also may parallel the underlying etiology of AMI found in patients with ORD. Prior studies have shown an association between elevated clotting factors and fibrinogen levels in opium consumption which may contribute to thromboembolic events leading to stroke or MI.[24] Therefore, prophylactic treatment with antithrombotic or anticoagulant agents may provide early benefits in young patients with ORD in the setting of ACS (online Table 4.2). In addition to thromboembolic events, arrhythmia related to opioid exposure may be contributing to death in this population as well, given the more frequent cardiac arrest seen in the ORD population.[25,26]

To date, the association between opioids and cardiovascular outcomes has largely been studied in the context of opium use.[13] Opium use is associated with increased all-cause mortality and cardiovascular death.[27] Direct links to increased inflammation and insulin resistance, as well as increased levels of novel markers such as C-reactive protein, apolipoprotein A/B, and lipoprotein (a), provide a biological foundation behind coronary artery disease and opium use.[24] Moreover, it is possible that plaque rupture could be precipitated by opioid withdrawal.[13]

While these aforementioned findings pertain to opium, there is also evidence linking current-day opioids to risk of ACS. For example, a nested case-control study from the UK's General Practice Research Database of 1.7 million patients showed an increased risk of MI (OR 1.28, 95% CI 1.19–1.37) in patients who received opioids for pain.[28] It is also known that psychosocial effects of addiction are associated with mental health disorders, other drug use, and sedentary lifestyle, which are all associated with poor cardiovascular outcomes.[29] Lastly, studies on morphine use during AMI demonstrate increased risk of mortality, suboptimal reperfusion success in STEMI, larger infarct size, and microvascular obstruction influenced by reduced absorption of antiplatelet therapies.[30] Our findings add to the body of evidence that ORD may result in worse hospital outcomes in ACS, and the management of ACS can be influenced by ORD. This may also explain the findings of increased cardiovascular death in patients with prescription opioids seen in a recent large cohort.[7]

The difference we observed in the use of diagnostic angiography and/or PCI demonstrates that patients with ORD are less

likely to receive evidence-based management of ACS. In fact, we found that patients with ORD are over 60% less likely to receive potentially life-saving treatment, even after accounting for confounding variables such as sepsis and respiratory failure. There are several potential explanations for these findings. First, patients with ORD had a higher prevalence of concurrent sepsis, respiratory failure, bleeding events, and comorbid substance use—which may preclude a necessary diagnostic procedure. Second, patients with ORD were younger and lacked other traditional cardiovascular risk factors. Third, these findings may reflect systematic bias among clinicians in the care of patients with ORD, including dismissal of pain symptoms.[31] Importantly, in our study, 98% of angiograms performed occurred on the day of presentation regardless of ORD status (online Figure 2). Therefore, if the physician did not suspect ACS on the day of presentation, it was unlikely that further cardiac workup would be performed. In addition, cardiologists may be less likely to perform procedures among patients with ORD due to an as of yet unfounded concern that patients with ORD would not adhere to antiplatelet regimens that are prescribed post-procedurally.[32,33] Fourth, patients with ORD may carry a certain burden of mistrust and may have declined procedures. Lastly, patients with ORD are more likely to have left the hospital AMA and such discharges seem to have contributed to differential management based on findings from the sensitivity analysis. While we are unable to catalog reasons for the AMA discharges in this sample, untreated opioid withdrawal is a common contributing factor highlighting a need to prioritize timely and appropriate treatment of underlying opioid use disorder with buprenorphine or methadone.[34] These explanations are important to address because ORD status did not increase in-hospital mortality in patients who underwent diagnostic angiography and/or PCI during the ACS hospitalization.

Limitations

There are notable limitations of this study. Reliance on diagnostic codes may lead to misclassification of ORD and ACS, especially if ACS or cardiac arrest occurred as a complication during hospitalization. Moreover, our sensitivity analyses reveal that type II MI may have been much more common in the ORD group. This is relevant because type II MI is not managed under the same guidelines as ACS. Moreover, the in-hospital mortality may reflect the underlying disease process separate from the cardiac manifestation. However, our extensive sensitivity analyses found that ORD status regardless of strict ACS definition led to fewer coronary angiography in patients < 75 years old and increased in-hospital mortality in patients < 65 years old. Also, our study lacks granular socioeconomic data of the population. Although the subgroup analysis did not reveal a difference in the primary outcome based on socioeconomic status, this variable was broadly defined using median household income from the patient's ZIP code. Social determinants of health such as education level, employment status, and social support structure are not captured in our dataset. Due to its observational nature, we are unable to assess how ORD relates to increased mortality in ACS, and the NIS does not provide the sequence of hospital events, rationale of management decisions, or medications administered. Due to the structure of the NIS dataset, there may be residual confounding variables that we were unable to add into the study, limiting the strength of our findings. For example, there was no way to determine the severity of the patient's presentation within a given diagnosis code. Lastly, our study is limited to inpatient outcomes and cannot appreciate readmission status or long-term outcomes.

Conclusion

The findings of our study inform current clinical practice in the setting of the worst opioid epidemic in US history. We report that ORD influences in-hospital outcomes of ACS. Overall, young patients are the most vulnerable as ORD in this group leads to an increase in in-hospital mortality and cardiac arrest particularly in the setting of STEMI. Measures to address opioid prescribing and addiction may influence patient outcomes, but further guidance on treating patients with ORD is crucial. Our findings highlight that the proper delivery of care to patients with ORD may require a concerted effort across specialties, including addiction medicine and cardiology.

Future guidelines that incorporate opioid use as a risk factor for ACS and the early use of medical therapies for patients not deemed candidates for catheterization may be necessary to protect this otherwise at-risk population.

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Corresponding Author: *Justin M. Pacor, MD; Section of General Internal Medicine, Department of Medicine, Yale School of Medicine, New Haven, CT, USA (e-mail: Justin.pacor@gmail.com).*

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Perspectives:

Competency in Medical Knowledge
Opioid use has been implicated in ischemic heart disease, and studies have shown its impact on the absorption of antiplatelet therapy in acute coronary syndrome.

Competency in Patient Care: *Opioid users are receiving differing management of acute coronary syndrome compared to non-opioid users and require a high index of suspicion from a multidisciplinary care team to address pain, addiction, and stigmas, in addition to guideline-directed therapy for acute coronary syndrome.*

Translational Outlook 1: *Although this is an observational study, a notable increase in mortality for opioid users in acute coronary syndrome requires a well-designed cohort study to look at underlying causes of death.*

Translational Outlook 2: *A high rate of deferral for coronary angiography in opioid users should be evaluated in larger registries such as the National Cardiovascular Data Registry (NCDR). Whether deferred patients received appropriate medical management should also be evaluated to assess improvement in inpatient outcomes.*

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