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The Evolving Burden of Drug Use Associated Infective Endocarditis in the United States

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Abstract

Background: The rise in the number of valve operations performed for infective endocarditis (IE) due to drug use is an important manifestation of the opioid epidemic. This study characterized national trends and outcomes of valve surgery for drug use-associated IE (DU-IE).

Methods: Adults undergoing valve surgery for active IE in The Society of Thoracic Surgeons Adult Cardiac Surgery Database between July 2011 and June 2018 were stratified as DU-IE and non-DU-IE. Trends and clinical profiles were analyzed. Early outcomes were assessed. The association of DU-IE with outcomes was analyzed with multivariable regression, adjusting for STS valve model covariates.

Results: There were 34,905 valve operations performed for IE, of which 33.7% were for DU-IE. DU-IE operations increased 2.7-fold during the study period. There was considerable regional variability in DU-IE operations ranging 28% to 58% of all IE surgeries in 2018, with highest rates observed in East South Central and South Atlantic regions. DU-IE patients were younger and had fewer cardiovascular comorbidities. Risk-adjusted major morbidity and in-hospital mortality were significantly higher in the DU-IE group. Redo valve procedures in DU-IE patients were associated with worse outcomes, compared with those receiving a first valve operation.

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Conclusions: Operations for DU-IE have increased sharply in the United States during the last several years exhibiting substantial regional variability. DU-IE patients have unique clinical profiles, and worse risk-adjusted outcomes. This demonstrates the significant impact of the opioid epidemic on endocarditis surgeries and punctuates the urgent need for multidisciplinary regional and national efforts to reverse this trend.

Graphical Abstract

Classification:

Valve surgery; Endocarditis; Illicit drug use; Outcomes

Infective endocarditis is a severe infection often involving the heart valves, which can occur as a result of injecting drugs. In the setting of the opioid epidemic in the United States (US), hospitalizations for IE associated with injection drug use have increased over the past decade [1–5]. Heart valve surgeries for the treatment of DU-IE have risen substantially as well, with estimates ranging as high as twelve-fold increase since 2007 [4,5]. Patients with DU-IE are younger with fewer chronic illnesses or comorbidities than those with non-drug use-associated IE (NDU-IE), though they have higher rates of repeat operations [6,7]. In one cohort of eight academic cardiac surgery practices, 30% of valve surgeries for DU-IE were for redo valve surgeries [8], which may in part be attributable to high rates of recurrent endocarditis [4,6,9–11].

Large-scale data about the clinical profile and outcomes of persons undergoing surgery for DU-IE has been limited. Existing studies have drawn from administrative datasets [5,12], that lack reliable data on clinical comorbidities and relevant surgical characteristics, single center studies [6,9,13] or small cohorts [8,11,14] that may impact generalizability.

We sought to definitively characterize the changing epidemiology and outcomes of those undergoing valve surgery for DU-IE in the US. We analyzed the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) to quantify valve surgeries for DU-IE, describe patient characteristics and evaluate early clinical outcomes.

Patients and Methods

Study Population

Data were assessed from the STS ACSD from July 2011 to June 2018. The study population included all patients >18 years of age undergoing valve surgery for active IE stratified into DU-IE and NDU-IE. DU-IE was defined as documented history of illicit drug use such as heroin, cocaine, or methamphetamine, or abuse of a controlled substance. Patients were excluded if information was not available for type of valve operation; if patient had an aortic procedure that did not also include aortic valve repair, replacement or root reconstruction/replacement; or if center had >10 cases with information missing for illicit drug use. This resulted in 34,905 cases from 1,000 centers.

Endpoints

The primary clinical endpoints were: (1) operative mortality, defined as all deaths within 30 days of surgery, both in and outside hospital, and in-hospital mortality; (2) in-hospital mortality, defined as death occurring during index hospitalization. The primary difference between these two endpoints is that operative mortality captures deaths within 30 days occurring after hospital discharge. Major postoperative complications were defined by STS major morbidity categories. Composite STS major morbidity was defined as occurrence of any of the following postoperative complications: deep sternal wound infection, renal failure, prolonged mechanical ventilation, reoperations, and stroke.

Statistical analysis

Baseline patient characteristics and outcomes were summarized by the percentage distribution for categorical variables and by medians and 25th and 75th percentiles for continuous variables. The prevalence and incidence of valve surgery for illicit drug use associated endocarditis was stratified by US census regions. Frequency of valve surgery and trend over time for illicit drug use and endocarditis culture was analyzed by multinomial baseline-category logit model treating year as linear variable. Risk adjustment was performed when comparing outcomes between DU and NDU using logistic regression modeling for each endpoint with adjustment using variables from the 2018 STS Valve Risk model [15]. When comparing primary and redo valve operations in the DU-IE cohort the same risk model was used except that redo was defined as previous valve operation. This study of deidentified data from the STS ACSD was granted a waiver of informed consent by the Duke University Institutional Review Board.

Results

Study Population and Trends

There were 34,905 surgeries for IE over the study period, of which 11,756 (33.7%) were for DU-IE and 23,149 (66.3%) were for NDU-IE. Overall IE surgeries increased by 1.7-fold during study period (Figure 1). This was driven most strongly by an increase in DU-IE cases, which increased 2.7-fold, while NDU-IE cases increased 1.4-fold over the period. DU-IE accounted for 24% of IE surgeries in 2011, and 38% in 2018 (Supplemental Table 1).

Regional Differences

The proportion of DU-IE among all IE operations increased in all regions from 2011 to 2018 (Figure 2). As of 2018, the regions with the greatest proportion of DU-IE were East South Central (58%), South Atlantic (45%) and New England (39%), while being least common in West North and South Central regions (28%) (Supplemental Table 2).

Patient Demographics and Preoperative Details

DU-IE patients were younger (median age 36 vs. 60 years) and less frequently male (62.2% vs. 68.9%), compared with NDU-IE (Table 1). Persons with DU-IE more commonly smoked cigarettes (74.4% vs. 20.3%), reported >7 drinks/week (12% vs. 7.6%) and had liver disease (46.3% vs. 9.4%). All other comorbidities were significantly less common among DU-IE. Insurance status also differed between the groups, with DU-IE predominantly insured by Medicaid (41.4%) or uninsured (19.7%) and NDU-IE typically insured by Medicare (38.0%) or commercial insurance (26.9%) (Supplemental Table 3).

Microbiology was significantly different between the two groups. While *Staphylococcus aureus* and *Streptococcus spp.* were the most common bacteria in both groups, *S. aureus* comprised 42.1% of DU-IE, compared with 24.3% of NDU-IE. Further, fungal endocarditis was more common among DU-IE (3.1%) than NDU-IE (1.5%).

Compared with NDU-IE, patients with DU-IE had lower prevalence of congestive heart failure and arrhythmia (Table 2). IE surgeries generally occurred on an urgent basis (80.4% overall), although NDU-IE surgeries were more commonly elective than DU-IE (12.2% vs. 8.5%) (Supplemental Table 3).

Operative Details

Overall, 73.9% of IE cases represented the first cardiovascular surgery for patients (Table 3). Aortic valve procedures were the most common in both DU-IE (44.7%) and NDU-IE (63.1%), followed by mitral valves (39.4% and 52.6%, respectively) and tricuspid valves (39.3% and 10.2%, respectively). Mitral valve replacement was slightly less common among DU-IE, compared with NDU-IE (72.5% vs 74.8%). DU-IE patients undergoing tricuspid surgery more commonly had replacements (57.6%) than NDU-IE patients (27.1%).

Outcomes

Although rates of all major morbidity indicators were significantly lower among DU-IE than NDU-IE, DU-IE patients had longer postoperative lengths of stay (median 12 vs. 10 days). Unadjusted operative and in-hospital mortality were also significantly lower among DU-IE (6.7% and 5.9%, respectively) than NDU-IE (33.4% v. 10.7%) (Table 4). However, in adjusted models, DU-IE was associated with higher odds of major morbidity (OR 1.11, 95% CI 1.03–1.19) and in-hospital mortality (OR 1.15, 95% CI 1.01–1.31). Operative mortality did not differ between the groups (OR 1.12, 95% CI 0.99–1.27) (Table 5).

In the DU-IE cohort, redo valve surgeries were 16.1% of all cases (Table 3). Unadjusted operative mortality, in-hospital mortality and major morbidity were significantly lower for primary valve surgeries (6.1%, 5.3%, and 33.9%, respectively) than redo valve surgery

(8.7%, 7.8%, and 37.1%, $p<0.001$). In the adjusted analysis, compared to DU-IE patients undergoing their first valve operation, DU-IE patients receiving redo valve surgery had higher odds of major morbidity (OR 1.25, 95% CI 1.10–1.42), operative mortality (OR 1.46, 95% CI 1.17–1.84), and in-hospital mortality (OR 1.51, 95% CI 1.19–1.91).

Comment

In this study of nearly 35,000 valve surgeries for IE occurring in the US, one-third were for drug use-associated IE (DU-IE), and the proportion has risen substantially since 2011. These results indicate that DU-IE is recasting the profile of patients undergoing surgery for IE and implore a fundamental shift in the care needs of patients with IE. Consistent with findings in previous cohorts, those with DU-IE were young, had fewer comorbidities and most frequently had infections with *Staphylococcus aureus* [6,8,9,16]. This changing epidemiology has not evenly impacted the US. In 2018, nearly 60% of valve surgeries for IE in the East South Central region were drug-related, and other hard-hit regions, such as South Atlantic and New England, have seen roughly 40% or higher of their IE surgeries to be drug-associated. Rates of risk-adjusted adverse outcomes were higher in patients undergoing valve operations for DU-IE.

Previous studies have suggested that patients with DU-IE appear to do well in the short term. These patients have low crude rates of in-hospital death, ranging from 2–6% in two recent studies of patients undergoing surgery [5,13]. In a meta-analysis of over 1,500 patients in thirteen observational studies, there was no difference in postoperative or in-hospital mortality between persons with DU-IE and those with IE due to other causes [17]. Accordingly, our study found that unadjusted rates of major morbidity, operative and in-hospital mortality were all lower among DU-IE. However, after adjusting for the extensive demographic and clinical factors that comprise the STS Valve Risk model, DU-IE were at higher odds of major morbidity and in-hospital mortality. In spite of their younger age and fewer comorbidities, DU-IE patients are at higher risk of adverse early outcomes after surgery.

Overall, the demographic, clinical and microbiologic profile of persons with DU-IE was markedly different than NDU-IE; most variables describing these populations in our study were substantially different between groups. DU-IE patients had a preponderance of tricuspid valve surgery, and more typically infections with *S. aureus*, which may be more virulent, or fungi, which may be more challenging to diagnose and eradicate. These factors were not captured in the present risk adjustment model but could conceivably modulate outcomes [18]. Therefore, comparisons between DU-IE and NDU-IE should be interpreted with caution and clinicians should tailor care to each patient's clinical picture.

Reoperative valve surgery was less common in the DU-IE group. Potential explanation includes reluctance to offer reoperative surgery for patient with active or prior drug use [19]. Among patients with DU-IE, those undergoing redo valve surgery had higher odds of adverse short-term outcomes, including mortality. This is consistent with recent cohort from eight academic centers where redo valve surgeries for DU-IE were associated with over a two-fold increased odds of 30-day mortality [8]. The lower magnitude observed in our study

may be the result of greater precision afforded by the analysis of a far larger cohort of surgeries, or it may suggest that patients undergoing care at academic centers harbor more complexity or greater risk.

Developing evidence-based guidelines can help direct providers in delivering high quality and consistent care for DU-IE. Studies have documented conflicting opinions among providers about the appropriate management of DU-IE and a perceived lack of transparency among providers with respect to surgical decision making [20]. Some centers have implemented endocarditis heart teams to evaluate patients' options and needs on a case-by-case basis with input from cardiac surgeons, infectious disease physicians, addiction medicine specialists, nurses and case workers [4,6].

National societies have called for the integration of inpatient addiction care for patients with IE, yet mounting evidence has documented that patients rarely receive the standard of care for addiction, especially in hospitals with less frequent DU-IE exposure [21–23]. In addition to conferring poor long-term outcome recurrent [13] or persistent drug use further complicates postoperative care. We observed significantly longer hospital stay in patients with DU-IE. Patients with IE require prolonged course of intravenous antimicrobials. Yet those with DU-IE are often not viewed as suitable candidates for outpatient parenteral antibiotic therapy and are therefore frequently kept for long periods in acute care hospitals to finish their treatment [4]. We found that the geography of areas most heavily impacted by DU-IE generally follows the Appalachian corridor that has been deeply impacted by drug overdoses and outbreaks of communicable diseases linked to injecting drugs [1,3,24]. The care of drug-related infections is expensive, resulting in high hospital charges, which may not be recouped by health systems. In West Virginia, across 8 years of DU-IE hospitalizations, only 22% of the over \$17,000,000 of hospital charges was actually collected [4, 25]. Our findings highlight the unique position of cardiac surgery teams to identify and intervene for this high-risk population. Time spent under the care of inpatient cardiac teams represents an important touchpoint to address substance use disorder (SUD) [4,20]. Beyond the dismal long-term outcomes after IE, patients may require care for overdose prevention, viral hepatitis or HIV as well as social services. In addition to providing good patient care, institutional investment in interventions, such as multidisciplinary teams lead by cardiac surgery and initiation of SUD treatment services, is a sensible approach. Such initiative may be successful in linking patients to outpatient SUD care, reducing preventable readmission and thereby improving patient outcomes and value.

The strengths of this study include the analysis of the largest sample of patients undergoing surgery for drug-related endocarditis during the current opioid crisis. This large sample size and the associated granular clinical data permitted the evaluation of outcomes, while adjusting for many relevant variables that are included in the STS Valve Risk Model. Additionally, observations were drawn from the STS ACSD, which has excellent penetration, estimated to capture >90–95% of hospitals that perform cardiac surgery in the US, as of 2019 [26].

Our study has several limitations. First, the definition of DU-IE was drawn from a variable on the STS data collection form, which is typically abstracted from the medical record.

Documentation of substance misuse in the medical record may be inconsistent or inaccurate, which could lead to misclassification of DU-IE. Second, the drug use variable has changed over the course of the study period. Prior to 2014, coders were instructed to select this variable if a patient had a history of marijuana use. Therefore, more patients may have been misclassified as DU-IE in the earlier study years due to marijuana use. Thirdly, documentation of the illicit drug use variable does not specifically distinguish between people who inject drugs and those who use drugs through other routes. While drug use can lead to health risks, drug injection is specifically linked to bloodborne infections [27]. Additionally, the proportion of centers participating in the STS ACSD may have changed over the course of the study period. However, as of 2012, it was estimated that the database captures 90% of centers performing cardiac surgery [28]. Lastly, we used the 2018 STS Valve Risk Model to evaluate clinical outcomes. This model, which accounts for numerous clinical factors, is not specifically optimized for infective endocarditis. Therefore, our analysis did not include potentially important factors, such as microbiology [18]. Endocarditis-specific models exist [29] and future studies should consider applying them to assess morbidity and mortality in cohorts of patients undergoing surgery for DU-IE.

Conclusion

Our results robustly demonstrate that substance use is reshaping the landscape of IE valve surgery in the US. The impact of this shift is not felt evenly across the US and, in certain regions, DU-IE now comprises a majority of IE valve surgeries. DU-IE have higher adjusted odds of early adverse outcomes. The regional differences in disease burden indicate that both interventions and funding must be tailored to local needs. Best practices in the multidisciplinary management of DU-IE and the development of regional and national preventative strategies are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Trends in Valve Surgeries for Infective Endocarditis, by Drug Use Status, 2011–2018. *July-December. **January-June.

Figure 2:
The Proportion of Valve Surgeries for Infective Endocarditis associated with Drug Use, by Region.

Table 1:**Patient Demographics, Clinical Factors and Microbiology**

Variable	Overall (n=34,905)	Drug Use (n=11,756)	No drug use (n=23,149)	p-value
Age (years, median, IQR)	53 (38–65)	36 (29–47)	60 (50–69)	<0.001
Male sex	23,271 (66.7%)	7,313 (62.2%)	15,958 (68.9%)	<0.001
Hypertension	19,971 (57.2%)	3,810 (32.4%)	16,161 (69.8%)	<0.001
Diabetes	8,896 (25.5%)	1,288 (11.0%)	7,608 (32.9%)	<0.001
Dialysis	4,538 (13.0%)	982 (8.4%)	3,556 (15.4%)	<0.001
Chronic lung disease	8,618 (24.7%)	2,744 (23.3%)	5,874 (25.4%)	<0.001
Cerebrovascular disease	10,508 (30.1%)	2,985 (25.4%)	7,523 (32.5%)	<0.001
Cerebrovascular accident	8,965 (25.7%)	2,721 (23.1%)	6,244 (27.0%)	<0.001
Cigarette smoking	13,445 (38.5%)	8,746 (74.4%)	4,699 (20.3%)	<0.001
Alcohol use				<0.001
<2 drinks/week	13,876 (39.8%)	3,594 (30.6%)	10,282 (44.4%)	
2–7 drinks/week	3,771 (10.8%)	1,355 (11.5%)	2,416 (10.4%)	
>7 drinks/week	3,168 (9.1%)	1,412 (12.0%)	1,756 (7.6%)	
Liver disease	7,616 (21.8%)	5,442 (46.3%)	2,174 (9.4%)	<0.001
Mediastinal radiation	323 (0.9%)	28 (0.2%)	295 (1.3%)	<0.001
Prior valve surgery	8,504 (24.4%)	2,021 (17.2%)	6,483 (28.0%)	<0.001
Microbiology				<0.001
Culture negative	3,623 (10.4%)	1,065 (9.1%)	2,558 (11.1%)	
<i>S. aureus</i> /MSSA/MRSA	10,566 (30.3%)	4,944 (42.1%)	5,622 (24.3%)	
<i>Streptococcus</i> species	9,200 (26.4%)	2,334 (19.9%)	6,866 (29.7%)	
Coagulase negative Staphylococci	1,441 (4.1%)	259 (2.2%)	1,182 (5.1%)	
Enterococcus	4,673 (13.4%)	1,437 (12.2%)	3,236 (14.0%)	
Fungal	712 (2.0%)	361 (3.1%)	351 (1.5%)	
Other	3,459 (9.9%)	1,028 (8.7%)	2,431 (10.5%)	

IQR, interquartile range; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

Table 2:**Preoperative Characteristics**

Variable	Overall (n=34,905)	Drug Use (n=11,756)	No drug use (n=23,149)	p-value
Cardiogenic shock	2,278 (6.5%)	729 (6.2%)	1,549 (6.7%)	0.082
Congestive heart failure	17,199 (49.3%)	5,033 (42.8%)	12,166 (52.6%)	<0.001
Ejection fraction				<0.001
<35%	1,371 (3.9%)	400 (3.4%)	971 (4.2%)	
35% and <45%	2,157 (6.2%)	642 (5.5%)	1,515 (6.5%)	
45% and <55%	5,062 (14.5%)	1,749 (14.9%)	3,313 (14.3%)	
55%	25,245 (72.3%)	8,614 (73.3%)	16,631 (71.8%)	
Aortic stenosis	4,728 (13.6%)	816 (6.9%)	3,912 (16.9%)	<0.001
Mitral stenosis	1,601 (4.6%)	364 (3.1%)	1,237 (5.3%)	<0.001
Tricuspid stenosis	355 (1.0%)	251 (2.1%)	104 (0.5%)	<0.001
Pulmonary stenosis	87 (0.3%)	27 (0.2%)	60 (0.3%)	0.60
Aortic insufficiency (moderate/severe)	14,186 (40.6%)	4,169 (35.5%)	10,017 (43.3%)	<0.001
Mitral insufficiency (moderate/severe)	14,895 (42.7%)	4,084 (34.7%)	10,811 (46.7%)	<0.001
Tricuspid insufficiency (moderate/severe)	8,545 (24.5%)	4,304 (36.6%)	4,241 (18.3%)	<0.001
Pulmonary insufficiency (moderate/severe)	523 (1.5%)	185 (1.6%)	338 (1.5%)	<0.001
Aortic root abscess	1,581 (4.5%)	417 (3.6%)	1,164 (5.0%)	<0.001
Arrhythmia (any)	9,473 (27.1%)	1,588 (13.5%)	7,885 (34.1%)	<0.001

IQR, interquartile range

Table 3:

Operative Characteristics

Variable	Overall (n=34,905)	Drug Use (n=11,756)	No drug use (n=23,149)	p-value
First cardiovascular surgery	25,782 (73.9%)	9,654 (82.1%)	16,128 (69.7%)	<0.001
Redo surgical valve procedure	6,563 (20.1%)	1,862 (16.1%)	4,701 (22.4%)	<0.001
Aortic valve procedure	19,854 (56.9%)	5,253 (44.7%)	14,601 (63.1%)	<0.001
Aortic valve procedure type				0.001
Replacement	16,162 (81.4%)	4,361 (83.0%)	11,801 (80.8%)	
Repair	354 (1.8%)	95 (1.8%)	259 (1.8%)	
Root replacement/reconstruction	3,338 (16.8%)	797 (15.2%)	2,541 (17.4%)	
Mitral valve procedure	16,808 (48.2%)	4,636 (39.4%)	12,172 (52.6%)	<0.001
Mitral valve procedure type				0.002
Repair	4,338 (25.8%)	1,274 (27.5%)	3,064 (25.2%)	
Replacement	12,470 (74.2%)	3,362 (72.5%)	9,108 (74.8%)	
Tricuspid valve procedure	6,982 (20.0%)	4,624 (39.3%)	2,358 (10.2%)	<0.001
Tricuspid valve procedure type				<0.001
Repair	3,381 (48.4%)	1,686 (36.5%)	1,695 (71.9%)	
Replacement	3,304 (47.3%)	2,664 (57.6%)	640 (27.1%)	
Valvectomy	297 (4.3%)	274 (5.9%)	23 (1.0%)	
Pulmonary valve procedure	281 (0.8%)	138 (1.2%)	143 (0.6%)	<0.001
Surgery type				<0.001
Isolated aortic valve procedure	13,022 (37.3%)	3,271 (27.8%)	9,751 (42.1%)	
Isolated mitral valve procedure	9,567 (27.4%)	2,492 (21.2%)	7,075 (30.6%)	
Isolated tricuspid valve procedure	3,979 (11.4%)	3,298 (28.1%)	681 (2.9%)	
Isolated pulmonary valve procedure	142 (0.4%)	74 (0.6%)	68 (0.3%)	
Multiple valve procedures	8,195 (23.5%)	2,621 (22.3%)	5,574 (24.1%)	

Table 4:

Early Outcomes of Surgery for Infective Endocarditis

Variable	Overall (n=34,905)	Drug use (n=11,756)	No drug use (n=23,149)	p-value
Postoperative length of stay (days, median, IQR)	10 (7–18)	12 (7–24)	10 (7–16)	<0.001
Major morbidity	13,341 (38.2%)	4,070 (34.6%)	9,271 (40.1%)	<0.001
Stroke	1,065 (3.1%)	272 (2.3%)	793 (3.4%)	<0.001
Reoperation	5,163 (14.8%)	1,665 (14.2%)	3,498 (15.1%)	0.018
Renal failure	3,067 (8.8%)	837 (7.1%)	2,230 (9.6%)	<0.001
Deep sternal wound infection	113 (0.3%)	28 (0.2%)	85 (0.4%)	0.045
Prolonged ventilation	10,945 (31.4%)	3,220 (27.4%)	7,725 (33.4%)	<0.001
Operative mortality	3,259 (9.3%)	783 (6.7%)	2,476 (10.7%)	<0.001
In-hospital mortality	2,927 (8.4%)	695 (5.9%)	2,232 (9.6%)	<0.001

IQR, interquartile range

Table 5:

Regression Analyses: Association of Drug Use-Associated Infective Endocarditis on Early Adverse Outcomes

Outcome	Unadjusted		Adjusted*	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Major morbidity	0.79 (0.75–0.84)	<0.001	1.11 (1.03–1.19)	0.007
Operative mortality	0.60 (0.55–0.65)	<0.001	1.12 (0.99–1.27)	0.076
In-hospital mortality	0.59 (0.54–0.64)	<0.001	1.15 (1.01–1.31)	0.037

OR, odds ratio. Reference: no drug use.

* Adjusted for covariates used in the 2018 STS Valve Risk Model