JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 8, 2024

PUBLISHED BY ELSEVIER

Infective Endocarditis in Patients Addicted to Injected Opioid Drugs

Michael J. Javorski, MD, MS,[a] Brad F. Rosinski, MD,[a] Shawn Shah, MD, MBA,[a] Matthew A. Thompson, BS, BA,[b] David Streem, MD,[c] Steven M. Gordon, MD,[d] Steven Insler, DO,[e] Penny L. Houghtaling, MS,[f] Brian Griffin, MD,[g] Eugene H. Blackstone, MD,[a,f] Shinya Unai, MD,[a] Lars G. Svensson, MD, PhD,[a] Gösta B. Pettersson, MD, PhD,[a] Haytham Elgharably, MD[a]

ABSTRACT

BACKGROUND Persons who inject drugs and require surgery for infective endocarditis have 2 potentially lethal diseases. Current postoperative rehabilitation efforts seem ineffective in preventing loss to follow-up, injection drug use relapse (relapse), and death.

OBJECTIVES The purpose of this study was to characterize drug use, psychosocial issues, surgical outcome, and postoperative addiction management, as well as loss to follow-up, relapse, and mortality and their risk factors.

METHODS From January 2010 to June 2020, 227 persons who inject drugs, age 36 ± 9.9 years, underwent surgery for infective endocarditis at a quaternary hospital having special interest in developing addiction management programs. Postsurgery loss to follow-up, relapse, and death were assessed as competing risks and risk factors identified parametrically and by machine learning. CIs are 68% (±1 SE).

RESULTS Heroin was the most self-reported drug injected (n = 183 [81%]). Psychosocial issues included homelessness (n = 56 [25%]), justice system involvement (n = 150 [66%]), depression (n = 118 [52%]), anxiety (n = 104 [46%]), and post-traumatic stress disorder (n = 33 [15%]). Four (1.8%) died in-hospital. Medication for opioid use disorder prescribed at discharge increased from 0% in 2010 to 100% in 2020. At 1 and 5 years, conditional probabilities of loss to follow-up were 16% (68% CI: 13%-22%) and 59% (68% CI: 44%-65%), relapse 32% (68% CI: 28%-34%) and 79% (68% CI: 74%-83%), and mortality 21% (68% CI: 18%-23%) and 68% (68% CI: 62%-72%). Younger age, heroin use, and lower education level were predictors of relapse.

CONCLUSIONS Infective endocarditis surgery can be performed with low mortality in persons who inject drugs, but addiction is far more lethal. Risk of loss to follow-up and relapse require more effective addiction strategies without which this major loss to society will continue. (J Am Coll Cardiol 2024;83:811–823) © 2024 by the American College of Cardiology Foundation.

Persons who inject drugs (PWID) and require surgery for related infective endocarditis have at least 2 lethal conditions. As opioid addiction has escalated to an epidemic in the United States,[1-3] injection drug use-associated infective endocarditis has also increased, presenting surgical, psychosocial, moral and ethical, and decision-making challenges.[4-6] These patients are young with few comorbidities, yet they present late in the course of endocarditis, and their operations are often complex and associated with complications, long hospital stays, and high health care costs.[7-9] Worse, however,

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio, USA; [b]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA; [c]Department of Psychiatry, Cleveland Clinic, Cleveland, Ohio, USA; [d]Department of Infectious Disease, Cleveland Clinic, Cleveland, Ohio, USA; [e]Department of Intensive Care and Resuscitation, Cleveland Clinic, Cleveland, Ohio, USA; [f]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, USA; and the [g]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 31, 2023; revised manuscript received November 17, 2023, accepted December 19, 2023.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2023.12.016

ABBREVIATIONS AND ACRONYMS

MOSAIC = Management of Substance Use Disorder and Heart Infections in Cardiovascular Patients

MOUD = medications for opioid use disorder

PWID = persons who inject drugs

SOAR = Supporting Opioid Addiction Recovery

long-term mortality is up to 10 times higher than if they did not inject drugs, because of drug relapse, overdose, and reinfection.[7,10-14] Prevention is thought to require a comprehensive holistic approach, but success is poor.[15]

We hypothesize that PWID have complex and interacting social, educational, legal, mental health, and other social determinants of health issues contributing to their addiction that are incompletely identified and accounted for. Therefore, to better inform strategies designed to prevent injection drug use relapse and death and improve clinical outcomes of endocarditis surgery, we conducted a single-center study of PWID undergoing cardiac surgery for infective endocarditis in the context of a quaternary hospital with particular interest in developing and implementing addiction management programs. Specific objectives were to study characteristics of drug use among these patients; their education level; their underlying social, justice-system, and mental health issues; their addiction management before and after surgery; and competing risks of becoming lost to follow-up, injection drug use relapse, and mortality.

SEE PAGE 824

METHODS

PATIENTS. From January 1, 2010, to June 1, 2020, 227 PWID, mean age 36 ± 9.9 years, 43% women, underwent cardiac surgery for infective endocarditis at Cleveland Clinic (Table 1). Patients were identified from institutional infective endocarditis registries coded for injection or intravenous drug use. The most common pathogen was *Staphylococcus aureus* followed by *Streptococcus viridans* and Enterococcus species (Table 1).

EVOLUTION OF ADDICTION MANAGEMENT. As opioid addiction became an epidemic, our philosophy and approach to addiction management evolved (Figure 1). Early in the study period, PWID with infective endocarditis referred for surgery were encouraged to agree to addiction treatment, verbally or by signing a nonbinding "contract," but resources and facilities available for treatment and rehabilitation were limited and remain so. During this period, many patients had a history of receiving medication for opioid use disorder (MOUD) before their endocarditis was diagnosed, having been seen by an addiction specialist, but they continued injecting and

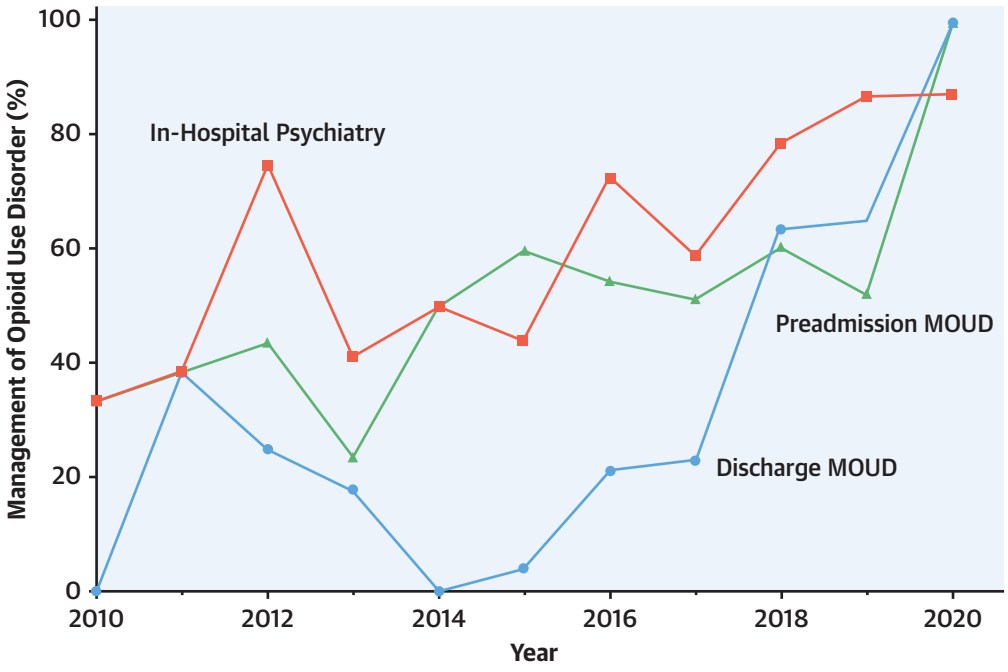
TABLE 1 Patient Characteristics, Operative Details, and Postoperative Complications

	n[a]	Mean ± SD or n (%)
Demographics		
Age, y	227	36 ± 9.9
Female	227	97 (42.7)
Body mass index, kg/m^2	227	24 ± 5.9
Race	219	
White		198 (90.4)
Black		13 (5.9)
Other		8 (3.7)
Medical history/comorbidities		
Prior cardiac surgery for infective endocarditis	227	67 (30.0)
Myocardial infarction	227	13 (5.7)
Atrial fibrillation/flutter	225	16 (7.1)
Complete heart block	218	9 (4.1)
Heart failure	225	70 (31.1)
Peripheral artery disease	227	14 (6.2)
Hypertension	227	82 (36.1)
COPD	227	35 (15.4)
Dialysis	226	19 (8.4)
Prior stroke	226	86 (38.0)
Dyslipidemia	226	40 (17.7)
Infective endocarditis organism	216	
Staphylococcus aureus		113 (52.3)
Coagulase-negative staphylococcus		2 (0.92)
Gram-positive cocci, not further identified		14 (6.5)
Viridans streptococcus		24 (11.1)
Enterococcus		21 (9.7)
Yeast/fungal		11 (5.1)
Other		13 (6.0)
Polymicrobial		14 (6.5)
Pathogen not identified		5 (2.3)
Operation		
Aortic valve surgery	227	109 (48.0)
Mitral valve surgery	227	101 (44.5)
Tricuspid valve surgery	227	125 (55.1)
Pulmonary valve surgery	227	4 (1.8)
AV/MV (left side) only	227	101 (44.5)
TV/PV (right side) only	227	68 (30.0)
AV/MV + TV	227	58 (25.6)
Aortic root, ascending or arch	227	60 (26.4)
Postoperative outcomes		
Hospital death	227	4 (1.8)
Operative mortality	225	7 (3.1)
Permanent stroke	227	4 (1.8)
New-onset renal failure[b]	207	5 (2.4)
Prolonged ventilation, >24 h	227	74 (32.6)
Long postoperative stay, >14 days	227	83 (36.6)

[a]Patients with data available. [b]Patients on preoperative dialysis are excluded from the denominator.

AV = aortic valve; COPD = chronic obstructive pulmonary disease; MV = mitral valve; PV = pulmonary valve; TV = tricuspid valve.

FIGURE 1 Evolution of Strategies for Managing Opioid Use Disorder



Proportion of persons who inject drugs and undergo surgery for infective endocarditis with any history of medication for opioid use disorder (MOUD) before surgery (green line and triangles), proportion evaluated by in-hospital psychiatry before surgery (red line and squares), and proportion receiving MOUD at hospital discharge (blue line and circles).

developed endocarditis. Our addiction program lacked enthusiasm for discharging patients on MOUD at that time. In-hospital psychiatric evaluation was somewhat erratic, but in 2015, driven by nursing, a specialized multidisciplinary addiction team began developing a program called MOSAIC (Management of Substance Abuse Disorder and Heart Infections in Cardiovascular Patients) that included standardized protocols for preoperative, perioperative, and postoperative care (see details in Supplemental Text 1). This program was fully deployed in 2020, with an electronic medical record dashboard implemented in 2021. In 2017, an Endocarditis Center was established and applied a multidisciplinary team approach to managing PWID presenting with infective endocarditis, including preoperative evaluation by a psychiatric addiction specialist along with a cardiologist, infectious disease specialist, and cardiac surgeon. Involvement of the Addiction Medicine team resulted in more frequent use of MOUD. That same year, our psychiatry group received privileges to see patients at a local rehabilitation center to improve postdischarge follow-up and management. In 2019, the State of Ohio launched Project SOAR (Supporting Opioid Addiction Recovery; see details in Supplemental Text 1). By the end of the study, nearly 100% of PWID with infective endocarditis were enrolled in MOSAIC and SOAR, and both preadmission and discharge MOUD reached 100%.

OPERATION FOR INFECTIVE ENDOCARDITIS. Patients underwent isolated or combined valve surgery involving the aortic valve in 48%, mitral valve in 44%, tricuspid valve in 55%, and pulmonary valve in 1.8% (**Table 1**). Infective endocarditis involved only left-sided valves in 44%, only right-sided in 30%, and both sides in 26%. A total of 67 procedures (30%) were reoperations; 7 a second reoperation, and 1 a third.

ENDPOINTS. Time-related primary endpoints were as follows: 1) becoming lost to follow-up; 2) injection drug use relapse (relapse); and 3) death, considered together as competing risks. Time of relapse was the first known relapse after infective endocarditis surgery. Secondary endpoints were postoperative in-hospital morbidity and mortality and recurrent infective endocarditis.

TABLE 2 Social, Educational, and Psychiatric Background

	n[a]	n (%)
Social		
Homelessness	226	56 (24.8)
Married	227	54 (23.8)
Single	227	139 (61.2)
Divorced	227	34 (15.0)
Children	227	154 (67.8)
Justice system involvement	227	150 (66.1)
Highest education level		
Grade school	184	11 (6.0)
Left high school before graduating	184	47 (25.5)
High school graduate/GED	184	115 (62.5)
College degree	184	8 (4.3)
Higher degree	184	3 (1.6)
Psychiatric history		
Depression	227	118 (52.0)
Anxiety	227	104 (45.8)
Post-traumatic stress disorder	227	33 (14.5)
Adverse childhood experiences	227	47 (20.7)
Medication-assisted treatment	227	118 (52.0)

[a]Patients with data available.
GED = graduate education development test.

Postoperative surveillance, with periodic patient contact, was part of our clinical treatment protocol. In addition, we conducted intensive cross-sectional follow-up beginning in February 2022 using all available contact information, with particular focus on patients who had been lost to surveillance. Patients' electronic medical records, including surveillance reports, provided information about known relapse, infective endocarditis recurrence and reoperation, and vital status (Supplemental Figure 1). Last, we searched for obituaries on the internet to identify deaths among those we had been unable to contact. *Lost to follow-up* was defined as inability to obtain information about the patient within 1 year of the common closing date of cross-sectional follow-up, February 2022.

DATA AND ETHICS. Endocarditis microbiology and patient demographics, comorbidities, procedural details, and postoperative complications were obtained from infectious disease and surgical registries maintained for quality reporting. Self-reported social and educational information, justice system involvement, and psychiatric and psychological history were extracted from patients' medical records. All data were approved for use in research by the Cleveland Clinic Institutional Review Board on June 19, 2020, with a waiver of informed consent (IRB #20-692).

DATA ANALYSIS. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute) and R version 4.0 (R Foundation for Statistical Computing). Categorical data are summarized as frequencies and percentages, and continuous variables as mean ± SD or equivalent 15th, 50th (median), and 85th percentiles when data were skewed. Time-related estimates are presented with 68% CIs, consistent with ±1 SE.

Time-related events. Time zero was the date of surgery for infective endocarditis. We believed that becoming lost to follow-up could lead to underestimating the probability of relapse and death. Therefore, becoming lost to follow-up, relapse, and mortality were assessed as competing states with potentially informative censoring. For each outcome, we estimated conditional probability using the method of Pepe and Mori (Supplemental Methods 1).[16,17]

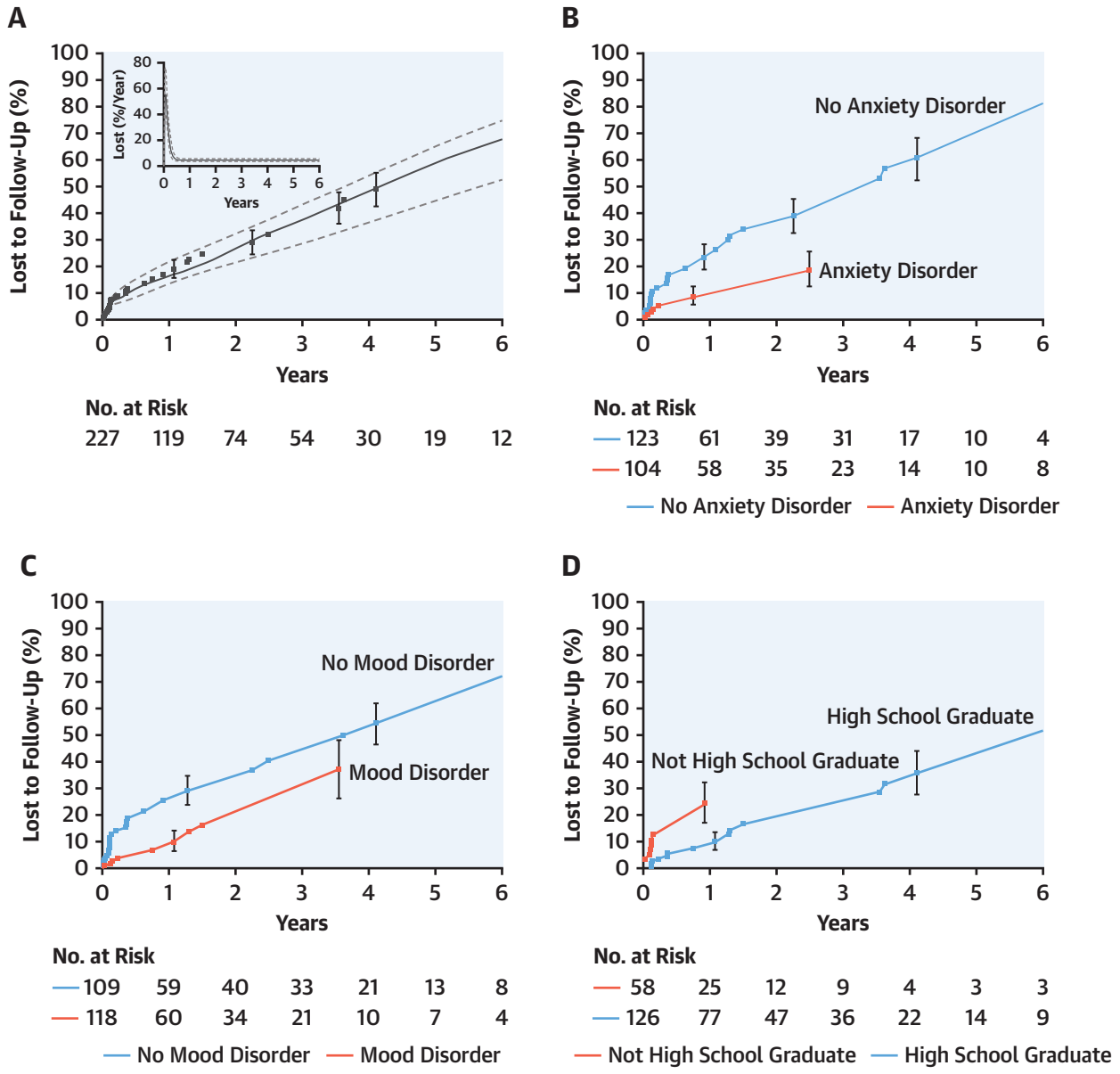
Risk factors for time-related events. To identify risk factors for time-related loss to follow-up, relapse, and mortality after surgery for infective endocarditis, 2 types of multivariable analyses were performed, details of which are presented in Supplemental Methods 2: a parametric multiphase temporal decomposition nonproportional hazard analysis,[18] with a machine-learning algorithm for variable selection[19] and a nonparametric analysis using RandomForestsSRC.[20] Variables considered in these multivariable analyses are listed in Supplemental Text 2.

RESULTS

DRUGS ABUSED AND PREOPERATIVE ADDICTION MANAGEMENT. Self-reported injection drugs being used when infective endocarditis occurred were heroin (183 [81%]), cocaine (60 [26%]), methamphetamine (35 [15%]), and other (34 [15%]). Previously, 118 patients had been treated with MOUD (eg, buprenorphine/naloxone; in 93 this information was missing). Postoperatively, discharge with MOUD reached 100% (**Figure 1**). Preoperatively, 144 were evaluated by in-hospital psychiatry, supported by the Alcohol and Drug Recovery Center, and this steadily increased after 2017 (**Figure 1**).

SOCIAL, JUSTICE SYSTEM, EDUCATIONAL, AND PSYCHIATRIC/PSYCHOLOGICAL FACTORS. One-fourth of patients reported being homeless at some point before surgery (**Table 2**). Two-thirds had justice system involvement (arrest, incarceration, or driving under the influence of alcohol). Highest education

FIGURE 2 Lost to Follow-Up After Surgery for Infective Endocarditis Among PWID



(A) Conditional probability of lost to follow-up after surgery for infective endocarditis among persons who inject drugs. Nonparametric probability estimates (symbols) are accompanied by 68% confidence bars (equivalent to ±1 SE), and the solid black line represents parametric estimates enclosed within a 68% dashed confidence band. Inset: Instantaneous risk (hazard function) of lost to follow-up. Solid line depicts parametric estimate enclosed within a 68% confidence band. (B to D) Unadjusted conditional probability with each symbol representing a patient lost to follow-up; vertical bars are 68% confidence limits. Effect of (B) anxiety disorder (P[log-rank] = 0.004), (C) mood disorder (P[log-rank] = 0.02), and (D) highest level of education (P[log-rank] = 0.03).

level was high school graduation in 63%, and 25% did not complete high school. Depression or other mood disorder was reported by 52% and anxiety disorder by 46%. In total, 21% of patients reported adverse childhood experiences. Post-traumatic stress disorder was reported by 14%.

SURGICAL OUTCOMES. In-hospital mortality was 1.8%, stroke 1.8%, and renal failure 2.4%, and prolonged ventilation >24 hours was 33% (Table 1). Median postoperative length of stay was 12 days. Both prolonged ventilation and long length of stay were due in part to withdrawal symptoms and pulmonary

TABLE 3 Risk Factors for Follow-Up Events After Surgery for Infective Endocarditis in Persons Who Inject Drugs

	Estimate ± SE	HR (95% CI)	*P* Value
Lost to follow-up			
Early increasing hazard phase			
No major depression or bipolar mood disorder	−1.43 ± 0.66	0.24 (0.06-0.88)	0.03
Not high school graduate	1.59 ± 0.78	4.9 (1.1-22)	0.04
Education missing/unknown	1.24 ± 0.60	3.5 (1.1-11)	0.04
Constant hazard phase			
No anxiety disorder	−1.72 ± 0.76	0.18 (0.04-0.79)	0.02
Relapse			
Early increasing hazard phase			
Not high school graduate	1.53 ± 0.74	4.6 (1.1-19)	0.04
Constant hazard phase			
Younger age	−0.051 ± 0.018	0.95 (0.92-0.98)	0.005
Heroin use[a]	1.4 ± 0.68	4.0 (1.1-15)	0.03
More recent date of surgery	0.164 ± 0.058	1.2 (1.05-1.3)	0.005
Death			
Early hazard phase			
Injection drug use relapse	2.5 ± 0.88	12 (1.9-78)	0.008
Time to relapse	0.028 ± 0.16	1.02 (0.75-1.4)	0.9

Estimates are based on a multivariable parametric analysis using multiphase hazard modeling. Education level was inversely proportional to risk of lost to follow-up and for relapse in the early phase. Age was inversely proportional to risk of relapse in the constant phase. Injection heroin use and more recent surgery date had a higher risk of relapse. For death, "injection drug use relapse" was entered as a time-varying covariate (patients who relapsed had a higher risk of early mortality, but time to relapse did not significantly affect survival).
[a]Self-reported heroin use may actually be any opioid and in recent years is primarily a fentanyl derivative with filler.

disease related to injection drug use. Prolonged hospitalization also related to difficulty in placing patients in rehabilitation facilities. In total, 147 patients (66%) were discharged to a skilled nursing or other medical facility (of whom 16 [11%] went to a facility with access to intensive outpatient addiction therapy); 68 (30%) were discharged home. A total of 19 recent patients (8.4% of those discharged) were enrolled in MOSAIC and 10 (4.4%) in SOAR.

The remaining 8 patients (3.6%) left against medical advice, 4 of whom had a relapse (3 died and 1 underwent reoperation for recurrent infective endocarditis during follow-up), 1 is alive without relapse, 1 is alive without relapse but presented back with pulmonary allograft stenosis, 1 has no records except for being incarcerated at one point, and 1 is lost to follow-up.

TIME-RELATED OUTCOMES. Lost to follow-up. A total of 36 patients were lost to follow-up after surgery, 6 immediately or within the first month after discharge, 1 of whom left against medical advice. Conditional probability of loss to follow-up at 6 months and 1, 3, and 5 years was 11% (68% CI: 8%-15%), 16% (68% CI: 13%-22%), 37% (68% CI: 28%-43%), and 59% (68% CI: 44%-65%), respectively (Figure 2A). Patients diagnosed with anxiety or mood disorders were less likely to be lost, as were patients with a higher education level (Table 3, Figures 2B to 2D, Supplemental Figure 2).

Injection drug use relapse. Of the 223 patients discharged, 103 were known to have injection drug use relapse by end of follow-up. Conditional probability of relapse at 6 months and 1, 3, and 5 years was estimated to be 13% (68% CI: 10%-16%), 32% (68% CI: 28%-34%), 62% (68% CI: 56%-65%), and 79% (68% CI: 74%-83%), respectively (Figure 3A). The highest relapse risk was within the first year, peaking at 40% per year at 9 months; after 2 years, risk was 17% per year (Figure 3A, inset). Younger age, injection heroin use (Figure 3B), and education level below high school graduate (Figure 3C) were risk factors for relapse (Table 3, Supplemental Figure 3). No trend was evident in prevalence of relapse across the study period (Figure 4).

Of the 103 who relapsed, 61 had recurrent infective endocarditis, 38 of whom underwent reoperation. Reasons for not undergoing repeat surgery were addiction treatment first (n = 11), not a surgical candidate because of severe comorbidities or multisystem organ failure (n = 6), patient not compliant or amenable to surgery (n = 2), death before surgical consideration (n = 1), or multiples of these reasons (n = 3).

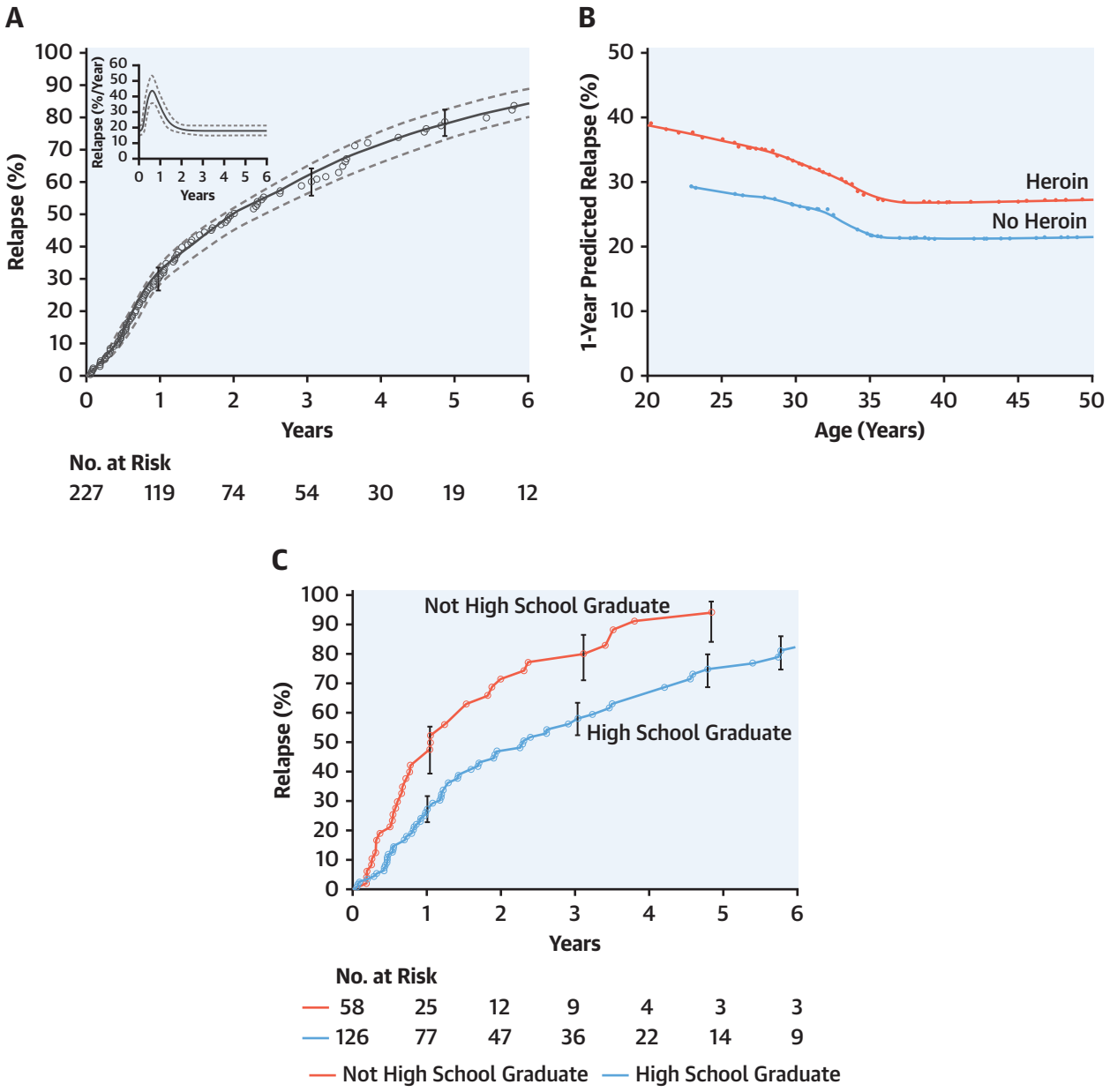
Death. During follow-up, 104 deaths were confirmed. Of these, 4 were hospital deaths after surgery. Mode of death was unknown in 69 (although 38 had known relapse after their most recent surgery), 17 from sequelae and complications of recurrent infective endocarditis associated with injection drug use, 4 from sequelae and complications of recurrent infective endocarditis not associated with known injection drug use, 3 from drug overdose, 4 from heart failure or cardiac arrest, and 3 from noncardiac causes.

Conditional probability of death at 6 months and 1, 3, and 5 years was estimated to be 11% (68% CI: 10%-13%), 21% (68% CI: 18%-23%), 48% (68% CI: 45%-50%), and 68% (68% CI: 62%-72%), with median time to death of 3.2 years (Figure 5A). Relapse was associated with early mortality (Table 3, Figure 5B); no other risk factor for death was identified.

DISCUSSION

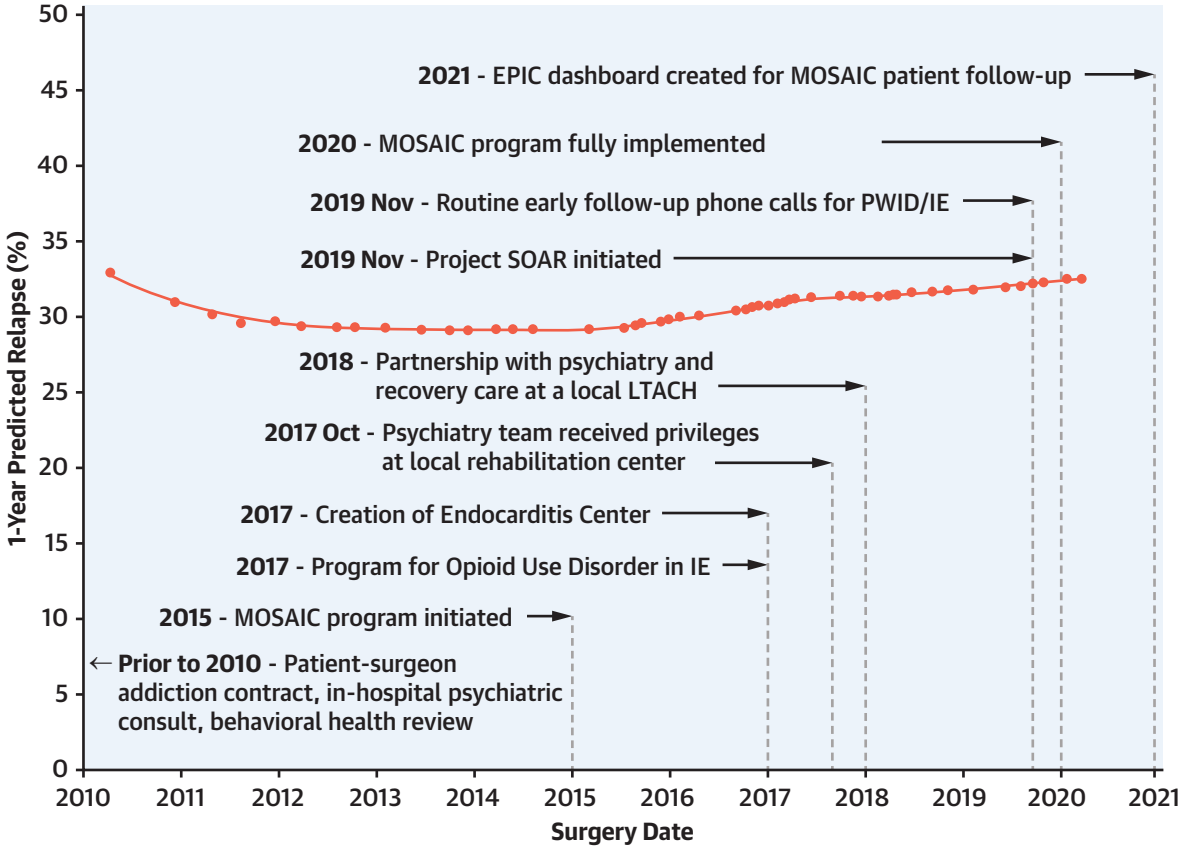
PRINCIPAL FINDINGS. The most common self-reported injection drug among PWID presenting with infective endocarditis requiring surgery was heroin, although the Ohio Department of Health and federal agencies have come to believe that "heroin" is now primarily a fentanyl derivative with fillers. Among these PWID, whose average age was 36 years, there was a high prevalence of psychosocial

FIGURE 3 Injection Drug Use Relapse After Surgery for Infective Endocarditis



(A) Conditional probability of injection drug use relapse after surgery for infective endocarditis among persons who inject drugs. Nonparametric conditional probability estimates (symbols) are accompanied by 68% confidence bars (equivalent to ±1 SE), and the solid black line represents parametric estimates enclosed within a 68% dashed confidence band. Inset: Instantaneous risk (hazard function) of relapse. Solid line depicts parametric estimate enclosed within a 68% confidence band. Two phases of risk were resolved: an early risk of relapse during the first year, peaking at 9 months at 42%/year (CI: 35%-50%), and a constant phase of risk after 2 years of 18%/year (CI: 15%-21%). (B) Effect of age and heroin use on 1-year conditional probability of injection drug use relapse. These are partial dependency plots from random forest competing risk analysis. Younger patients with injection heroin use had the highest 1-year relapse. Note that when people self-report heroin use, this may actually be any opioid and in recent years is primarily a fentanyl derivative with filler. Symbols are spaced at every 2 percentiles of age at which risk-adjusted estimates were made. (C) Effect of education on conditional probability of injection drug use relapse. Unadjusted estimates are stratified by highest level of education (P[log-rank] = 0.001). Each symbol represents a relapse, and vertical bars are 68% confidence limits.

FIGURE 4 Injection Drug Use Relapse and Timeline of Initiating Addiction Programs



Partial dependency graph of conditional probability of 1-year injection drug use relapse. Superimposed are the many initiatives introduced in attempting to rehabilitate patients who inject drugs (PWID) before and after their surgery for infective endocarditis (IE). These seem to have had little effectiveness in preventing relapse. LTACH = long-term acute care hospital; MOSAIC = Management of Substance Use Disorder and Heart Infections in Cardiovascular Patients; SOAR = Supporting Opioid Addiction Recovery.

comorbidities. After surgery, follow-up was challenging, with many becoming lost to follow-up surveillance; we determined that this led to underestimation of injection drug use relapse and an even greater underestimation of mortality (see Supplemental Methods 1). Injection drug use relapse postsurgery was high, and mortality was astonishingly high in this young patient population and similar to what we had observed in an earlier cohort.[10] The highest risk for relapse occurred within the first year after surgery. Despite our evolving addiction treatment and surveillance strategies over the decade, our analyses indicate that injection drug use continues unabated (**Central Illustration**). Thus, of the 2 lethal diseases—opioid addiction and infective endocarditis—we sadly report that opioid addiction was more lethal than advanced infective endocarditis treated with surgery.

Implications of loss to follow-up. Despite all efforts to track these patients, many became untraceable. Thus, accurate estimates of prevalence of relapse, infective endocarditis recurrence, and death from overdose are compromised. Therefore, we incorporated lost to follow-up as a separate event in a competing-risks analysis to estimate the conditional probability of relapse and death had patients not been lost. This revealed that death, even more than injection drug use relapse, was likely substantially underrepresented (see Supplemental Methods 1).

Implications of relapse. Although relapse is high by 5 years after surgery, the most important finding was that risk of relapse peaked at 9 months

postoperatively. With a multifaceted problem like fighting injection drug use and addiction, it suggests focusing close clinical follow-up efforts on this vulnerable first year after surgery. Specifically, during that time, our data suggest that these patients should be offered rehabilitation, medication assistance, psychiatric counseling, medication for mood or anxiety disorders, homelife assessment to ensure a safe home environment and family support, and close follow-up with a member of the endocarditis team.

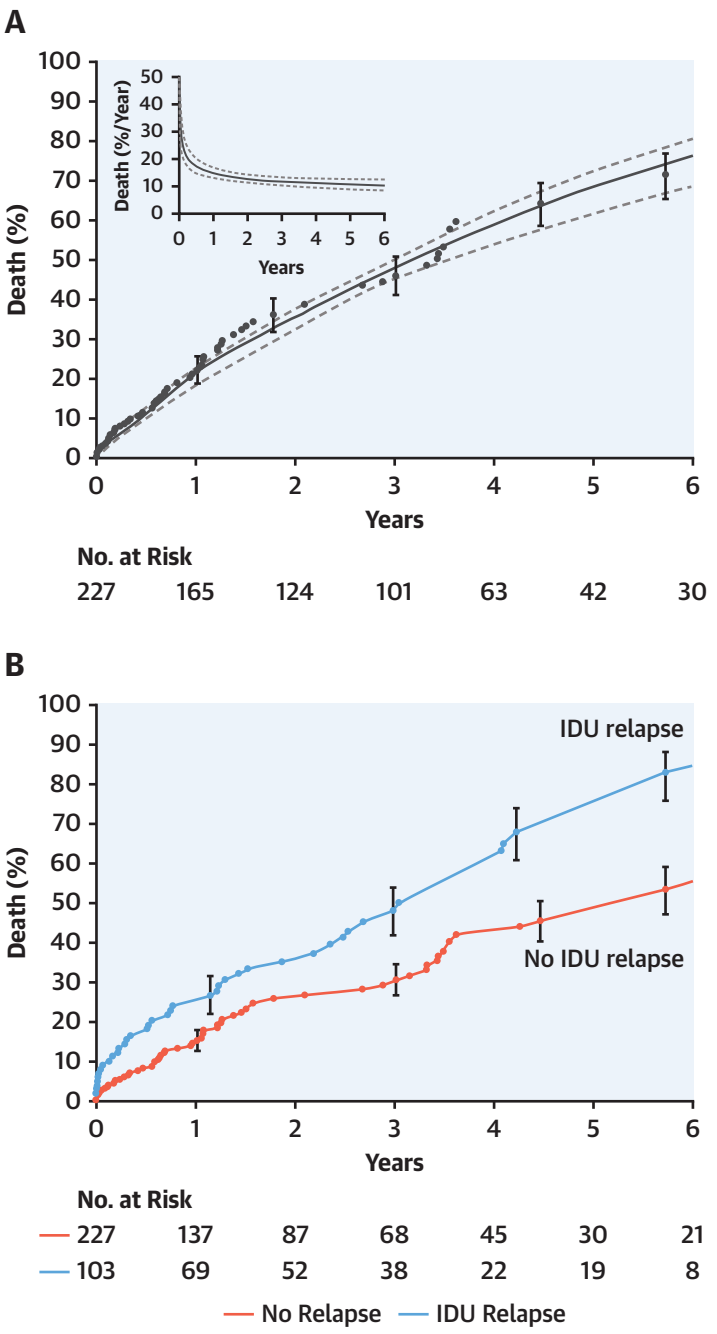
Younger age, heroin use, and education level below high school graduate were predictors of relapse.[21] These factors can help identify patients at highest risk of relapse, who may require a tailored care plan that includes addressing addiction first, if clinically possible.

Implications of death. The 5-year mortality among these young patients was shocking and was no better now than in our earlier study.[10] Usually, the mode of death could not be determined, but almost one-half of such patients had known relapse. It is reasonable to infer that the major cause of unknown deaths was fatal injection drug overdose or complications from recurrent infective endocarditis caused by injection drug use.[7]

COMPLEXITY OF SIMULTANEOUSLY TREATING 2 POTENTIALLY LETHAL DISEASES. The American Association for Thoracic Surgery guidelines indicate that ideally, patients with infective endocarditis should be cared for at centers with a comprehensive endocarditis team.[22] Early outcomes in the current study are excellent and are equivalent to those of patients without opioid addiction. Given these results, Baldassarri et al[6] argue that surgery for infective endocarditis in this setting, like any other setting, is generally not futile, and therefore it is not ethical to withhold surgery, even if there is a high likelihood of recidivism leading to recurrent endocarditis and reoperations.

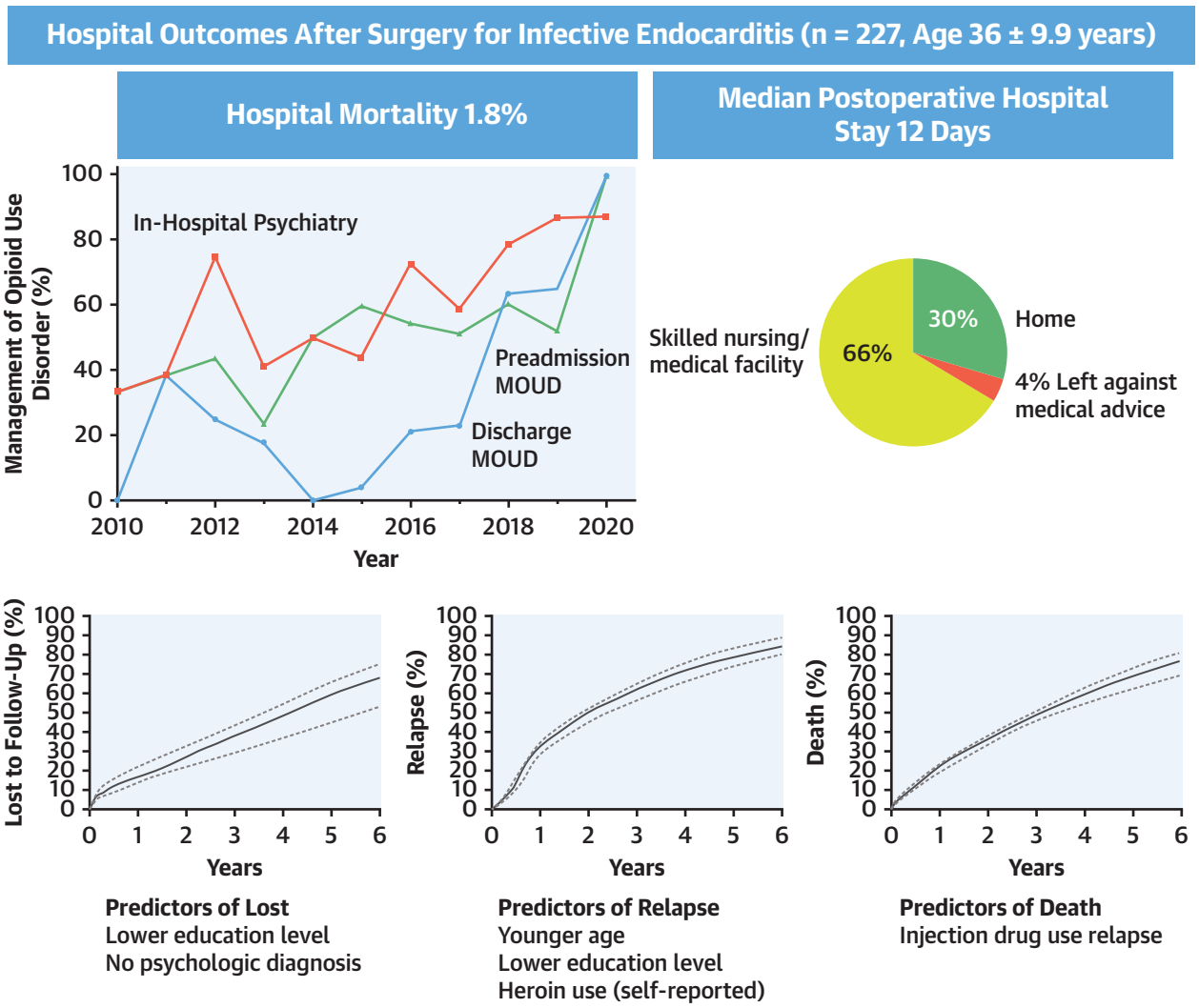
In contrast to successful surgical treatment of infective endocarditis, addiction to injection drugs is difficult to treat successfully and is compounded by social issues and psychiatric/psychologic illnesses. We have believed that a holistic approach by an engaged multidisciplinary team is needed to address all aspects and issues, with goals of maintaining surveillance, preventing relapse and thereby avoiding infective endocarditis recurrence, and keeping these patients alive. This has included addiction/substance use disorder evaluation by an addiction specialist from the psychiatry team, perioperative pain control, and postoperative addiction treatment and rehabilitation planning.

FIGURE 5 Death After Surgery for Infective Endocarditis Among PWID



(A) Time-related conditional probability of mortality after surgery for infective endocarditis in persons who inject drugs (PWID). Nonparametric probability estimates (symbols) are accompanied by 68% confidence bars (equivalent to ±1 SE), and parametric estimates are enclosed within 68% dashed confidence bands. Number of patients at risk is shown below horizontal axis. Inset: Instantaneous risk (hazard function) of death. Solid line depicts parametric estimate enclosed within a 68% confidence band. (B) Effect of injection drug use relapse on mortality as a time-related variable. These are unadjusted cumulative probability curves. For the blue line, time zero is the time of surgery; for the red line, time zero is time of relapse. Each symbol represents a death, and vertical bars are 68% confidence limits. IDU = injection drug use.

CENTRAL ILLUSTRATION **Management and Fate of Persons With Infective Endocarditis Who Inject Drugs: 2 Lethal Diseases**



Javorski MJ, et al. J Am Coll Cardiol. 2024;83(8):811-823.

Management of persons who inject drugs and have infective endocarditis—2 potentially lethal diseases—has evolved over time. Shown are timelines for any history of medication for opioid use disorder (MOUD) before surgery for infective endocarditis, the proportion evaluated by in-hospital psychiatry before surgery in red, and the proportion receiving MOUD at hospital discharge in blue. At hospital discharge, few have been discharged to home; most have gone to extended care and rehabilitation facilities. Three competing risks then attend these patients after surgery: 1) they become lost to follow-up (26% by 5 years); 2) they have injection drug use relapse (79% by 5 years) and with that recurrent endocarditis; and 3) they die (64% by 5 years). Risk factors are dominated by psychosocial issues, such that we conclude that surgery for infective endocarditis is quite safe; it is infection drug use that is killing them in what should be the prime of life (average age at presentation is 36 years).

However, our results are depressing! As evidenced by the timelines presented in Figure 3, our progressive introduction of more and more of these supportive elements[23-25] has provided no evidence of preventing either relapse or death.

IS THERE A WAY FORWARD? Preoperative planning. We are considering a "bridge to surgery" approach for stable patients presenting with right-sided endocarditis,[26] addressing the addiction first, use of antibiotics, and close follow-up. The rationale is, first, that right-sided endocarditis tends not to be invasive; and second, that addressing addiction before surgery combined with rehabilitation services postoperatively and close follow-up may reduce

early postoperative relapse, particularly in those at high risk of relapse.

Postoperative planning. Discharging PWID with MOUD after surgery for infective endocarditis has been reported to be of small or no mortality benefit.[27,28] However, meta-analysis of PWID without infective endocarditis demonstrates benefit.[29] In our study, use of MOUD at discharge was not predictive of preventing relapse. Yet, previous studies on MOUD[29-31] and anecdotal feedback from our follow-up study suggest that MOUD has been an effective resource for some patients, and thus it is worthwhile to continue the program. However, not all hospitals offer this.[31,32]

Discharge to rehabilitation facilities with addiction therapy competence is also hoped to improve outcomes.[33] Such programs are new in Ohio; hence, this resource is not frequently available to us. Harm reduction programs, eg, naloxone in multiple venues, are another resource that may prevent overdose and death.[34] Nevertheless, there remain numerous barriers to addiction recovery—personal, health care, and societal—that need to be addressed at each level.[35]

At this point, it is too early to know if our internal MOSAIC and State of Ohio SOAR programs will prove to be effective. Results of this study suggest that the programs should refocus on the first postoperative year.

Risk factors include younger age and lower educational status, suggesting that it may be valuable to develop community or sponsored outreach that offers focused therapy for these patients after discharge, including education, job training, counseling, and care in a halfway house setting. This would require financial support but might be something in which communities and business leaders would be willing to invest.

STUDY LIMITATIONS. Generalization from our study is limited by its observational nature from a single institution. The self-reported psychiatric/psychologic conditions reported were accepted as documented in the medical record, and categorization may not be in accord with criteria of the Diagnostic and Statistical Manual of Mental Disorders.[36] Unfortunately, we do not have the initiating event for opioid addiction, eg, whether it was related to prescriptions for pain. The unusual and extreme difficulty of achieving complete follow-up is not only a limitation but also an important finding. The information we have does not include possible periods of noncompliance before last follow-up or verified relapse. Accurate categorization of modes of death was difficult.

CONCLUSIONS

For PWID with infective endocarditis requiring surgery, the addiction is far more lethal than infective endocarditis alone. With underlying social, educational, and psychiatric/psychologic issues, the combination led to an astonishingly high mortality in these young individuals, unabated from our earlier study, despite effective surgery for infective endocarditis performed with low mortality.

Although our strategies and efforts to prevent injection drug use relapse for PWID in this study timeframe seem ineffective, we continue to believe it is possible to do better. A treatment algorithm must include a multidisciplinary team that can address addiction and all underlying psychosocial issues, discharge planning, consideration of MOUD, treatment of psychiatric or psychologic disorders, choosing a rehabilitation facility with access to outpatient intensive addiction therapy, search for a safe environment after the rehabilitation facility, and close follow-up, especially during the first postoperative year. Time will tell if the described current and new strategies are more effective than those of the past. Without more effective programs, we will continue to experience a major loss to society of individuals in their prime of life.

ACKNOWLEDGMENTS The authors thank Mary McLaughlin Davis, DNP, director of the social worker team, and Betsy Stovsky, RN, MSN, from the MOSAIC program, for their contribution to this study. Ms McLaughlin-Davis was instrumental in identifying the nursing facilities to which the patients went after discharge, and identifying which facilities offer intensive outpatient addiction therapy. Ms Stovsky is the key individual who helped coordinate the collaboration of the MOSAIC team and their resources with the research team.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Support was provided by the Drs Sidney and Becca Fleischer Heart and Vascular Education Chair (to Dr Blackstone), The Peter and Elizabeth C. Tower Family Endowed Chair in Cardiothoracic Research (to Dr Unai), James and Sharon Kennedy, The Slosburg Family Charitable Trust, and The Stephen and Saundra Spencer Fund for Cardiothoracic Research. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Haytham Elgharably, Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic, 9500 Euclid Avenue, Desk J4-1, Cleveland, Ohio 44195, USA. E-mail: Elgharh@ccf.org.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with a history of injected drug use, the first year after successful surgery for infective endocarditis is associated with high risks of relapse to opioid use, loss to follow-up, recurrent infection, and death caused by overdose or cardiac complications.

TRANSLATIONAL OUTLOOK: Greater efforts are needed to provide patients having a history of injected drug use with rehabilitation, psychological counseling, pharmacotherapy for psychiatric disorders, and social services to ensure a safe home environment, family support, and close medical follow-up after treatment of infective endocarditis.

REFERENCES

1. Centers for Disease Control and Prevention. Drug Overdose Deaths in the U.S. Top 100,000 Annually. National Center for Health Statistics. Published November 17, 2021. Accessed May 1, 2022. https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

2. Alnabelsi TS, Sinner G, Al-Abdouh A, et al. The evolving trends in infective endocarditis and determinants of mortality: a 10-year experience from a tertiary care epicenter. *Curr Probl Cardiol*. 2023;48(6):101673.

3. Rudasill SE, Sanaiha Y, Mardock AL, et al. Clinical outcomes of infective endocarditis in injection drug users. *J Am Coll Cardiol*. 2019;73(5):559–570.

4. Kadri AN, Wilner B, Hernandez AV, et al. Geographic trends, patient characteristics, and outcomes of infective endocarditis associated with drug abuse in the United States from 2002 to 2016. *J Am Heart Assoc*. 2019;8(19):e012969.

5. Bhandari R, Alexander T, Annie FH, et al. Steep rise in drug use-associated infective endocarditis in West Virginia: characteristics and healthcare utilization. *PLoS One*. 2022;17(7):e0271510.

6. Baldassarri SR, Lee I, Latham SR, D'Onofrio G. Debating medical utility, not futility: ethical dilemmas in treating critically ill people who use injection drugs. *J Law Med Ethics*. 2018;46(2):241–251.

7. Nguemeni Tiako MJ, Mori M, Bin Mahmood SU, et al. Recidivism is the leading cause of death among intravenous drug users who underwent cardiac surgery for infective endocarditis. *Semin Thorac Cardiovasc Surg*. 2019;31(1):40–45.

8. Dewan KC, Dewan KS, Idrees JJ, et al. Trends and outcomes of cardiovascular surgery in patients with opioid use disorders. *JAMA Surg*. 2019;154(3):232–240.

9. Geirsson A, Schranz A, Jawitz O, et al. The evolving burden of drug use associated infective endocarditis in the United States. *Ann Thorac Surg*. 2020;110(4):1185–1192.

10. Shrestha NK, Jue J, Hussain ST, et al. Injection drug use and outcomes after surgical intervention for infective endocarditis. *Ann Thorac Surg*. 2015;100(3):875–882.

11. Bearpark L, Sartipy U, Franco-Cereceda A, Glaser N. Surgery for endocarditis in intravenous drug users. *Ann Thorac Surg*. 2021;112(2):573–581.

12. Kim JB, Ejiofor JI, Yammine M, et al. Surgical outcomes of infective endocarditis among intravenous drug users. *J Thorac Cardiovasc Surg*. 2016;152(3):832–841.e831.

13. Osterdal OB, Salminen PR, Jordal S, Sjursen H, Wendelbo O, Haaverstad R. Cardiac surgery for infective endocarditis in patients with intravenous drug use. *Interact Cardiovasc Thorac Surg*. 2016;22(5):633–640.

14. Rodger L, Shah M, Shojaei E, Hosseini S, Koivu S, Silverman M. Recurrent endocarditis in persons who inject drugs. *Open Forum Infect Dis*. 2019;6(10):ofz396.

15. Elbatarny M, Bahji A, Bisleri G, Hamilton A. Management of endocarditis among persons who inject drugs: A narrative review of surgical and psychiatric approaches and controversies. *Gen. Hosp. Psychiatry*. 2019:5744–5749.

16. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? *Stat Med*. 1993;12(8):737–751.

17. Rajeswaran J, Blackstone EH. Competing risks: Competing questions. *J Thorac Cardiovasc Surg*. 2017;153(6):1432–1433.

18. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615–624.

19. Rajeswaran J, Blackstone EH. Identifying risk factors: challenges of separating signal from noise. *J Thorac Cardiovasc Surg*. 2017;153(5):1136–1138.

20. Ishwaran H, Kogalar UB. Unified Random Forests for Survival, Regression, and Classification (RF-SRC), R package version 2.9.3. Accessed December 26, 2023. http://cran.r-project.org/web/packages/randomForestSRC/index.html

21. Evans JL, Hahn JA, Lum PJ, Stein ES, Page K. Predictors of injection drug use cessation and relapse in a prospective cohort of young injection drug users in San Francisco, CA (UFO Study). *Drug Alcohol Depend*. 2009;101(3):152–157.

22. Pettersson GB, Coselli JS, Hussain ST, et al. 2016 American Association for Thoracic Surgery (AATS) consensus guidelines: surgical treatment of infective endocarditis. Executive summary. *J Thorac Cardiovasc Surg*. 2017;153(6):1241–1258.e1229. https://doi.org/10.1016/j.jtcvs.2016.1209.1093

23. Baddour LM, Weimer MB, Wurcel AG, et al. Management of infective endocarditis in people who inject drugs: a scientific statement from the American Heart Association. *Circulation*. 2022;146(14):e187–e201.

24. Yucel E, Bearnot B, Paras ML, et al. Diagnosis and management of infective endocarditis in people who inject drugs: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79(20):2037–2057.

25. Cortes-Penfield N, Cawcutt K, Alexander BT, Karre VMM, Balasanova AA. A proposal for addiction and infectious diseases specialist collaboration to improve care for patients with opioid use disorder and injection drug use-associated infective endocarditis. *J Addict Med*. 2022;16(4):392–395.

26. Witten JC, Hussain ST, Shrestha NK, et al. Surgical treatment of right-sided infective endocarditis. *J Thorac Cardiovasc Surg*. 2019;157(4):1418–1427.

27. Kimmel SD, Walley AY, Li Y, et al. Association of treatment with medications for opioid use disorder with mortality after hospitalization for injection drug use-associated infective endocarditis. *JAMA Netw Open*. 2020;3(10):e2016228.

28. Nguemeni Tiako MJ, Hong S, Bin Mahmood SU, et al. Inconsistent addiction treatment for patients undergoing cardiac surgery for injection drug use-associated infective endocarditis. *J Addict Med*. 2020;14(6):e350–e354.

29. Ma J, Bao YP, Wang RJ, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. *Mol Psychiatry*. 2019;24(12):1868–1883.

30. Lee JD, Friedmann PD, Kinlock TW, et al. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. *N Engl J Med*. 2016;374(13):1232–1242.

31. Brothers TD, Mosseler K, Kirkland S, Melanson P, Barrett L, Webster D. Unequal access to opioid agonist treatment and sterile injecting equipment among hospitalized patients with injection drug use-associated infective endocarditis. *PLoS One*. 2022;17(1):e0263156.

32. Nguemeni Tiako MJ, Mszar R, Brooks C 2nd, et al. Cardiac surgeons' practices and attitudes toward addiction care for patients with substance use disorders. *Subst Abus*. 2022;43(1):206–211.

33. Upadhyaya A, Marks LR, Schwarz ES, Liang SY, Durkin MJ, Liss DB. Care cascade for patients with opioid use disorder and serious injection related infections. *Toxicol Commun*. 2021;5(1):6–10.

34. Hervera B, Seo G, Bartholomew TS, et al. Implementation of an integrated infectious disease and substance use disorder team for injection drug use-associated infections: a qualitative study. *Addict Sci Clin Pract*. 2023;18(1):8.

35. Colwill JP, Sherman MI, Siedlecki SL, Burchill CN, Siegmund LA. A grounded theory approach to the care experience of patients with intravenous drug use/abuse-related endocarditis. *Appl Nurs Res*. 2021;57:151390.

36. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Publishing, Inc; 2013.

KEY WORDS cardiac surgery, competing risks, injection drug use, intravenous drug use, relapse

APPENDIX For an expanded Methods section and supplemental figures, please see the online version of this paper.