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MAJOR ARTICLE

Infective Endocarditis in People Who Inject Drugs—A 5-Year Follow-up: "I've Seen the Needle and the Damage Done"

Mika Halavaara,[1] Veli-Jukka Anttila,[1] and Asko Järvinen[1]

[1]Department of Infectious Diseases, Inflammation Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Background. Infective endocarditis (IE) among people who inject drugs (PWID) has been associated with better short-term outcome. Long-term outcome of PWID with IE is poorly known.

Methods. This retrospective population-based study included PWID with IE and non-PWID adults with community-acquired IE who were diagnosed and treated in Southern Finland between 2013 and 2017 and survived the initial IE episode. All patients were followed for 5 years. Data were collected on drug use, receipt of medications for opioid use disorder (MOUD), survival, and subsequent IE episode during follow-up.

Results. Seventy-five PWID with IE and 98 patients with community-acquired IE were included. Buprenorphine and amphetamine or other stimulant were the most used substances among PWID. Sixteen PWID received MOUD before onset of IE, and 33 received MOUD at the time of discharge. Most PWID (86%) received addiction specialist consultation during the hospitalization. Fifteen patients in the PWID IE group experienced a new IE episode within 5-year follow-up as compared with 5 patients in the non-PWID IE group (odds ratio [OR], 4.65; $P = .003$). One-year all-cause mortality was 4.0% (3/75) in PWID IE and 4.1% (4/98) in non-PWID IE. Five-year all-cause mortality was 18.7% (14/75) in PWID IE and 13.3% (13/98) in non-PWID IE ($P = .399$). In multivariate analysis of the whole group, injection drug use (OR, 12.2), female gender (OR, 2.62), and higher age-adjusted comorbidity index were independent factors associated with death during 5-year follow-up.

Conclusions. Long-term survival of PWID with IE is poor, and they are at increased risk of a new IE episode as compared with non-PWID with community-acquired IE. More efforts in the treatment of addiction are needed.

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From "*The needle and the damage done*" written by Neil Young and released in 1972 on album *Harvest*. It is a song about harms of drug addiction and injection drug use of musicians Neil Young knew.

Correspondence: Mika Halavaara, MD, PhD, Inflammation Center, Triangle Hospital, First Floor, Open-Plan Office, PO Box 00029 HUS, Helsinki, Finland (mika.halavaara@hus.fi); Asko Järvinen, MD, PhD, Inflammation Center, Triangle Hospital, First Floor, Open-Plan Office, PO Box 00029 HUS, Helsinki, Finland (asko.jarvinen@hus.fi).

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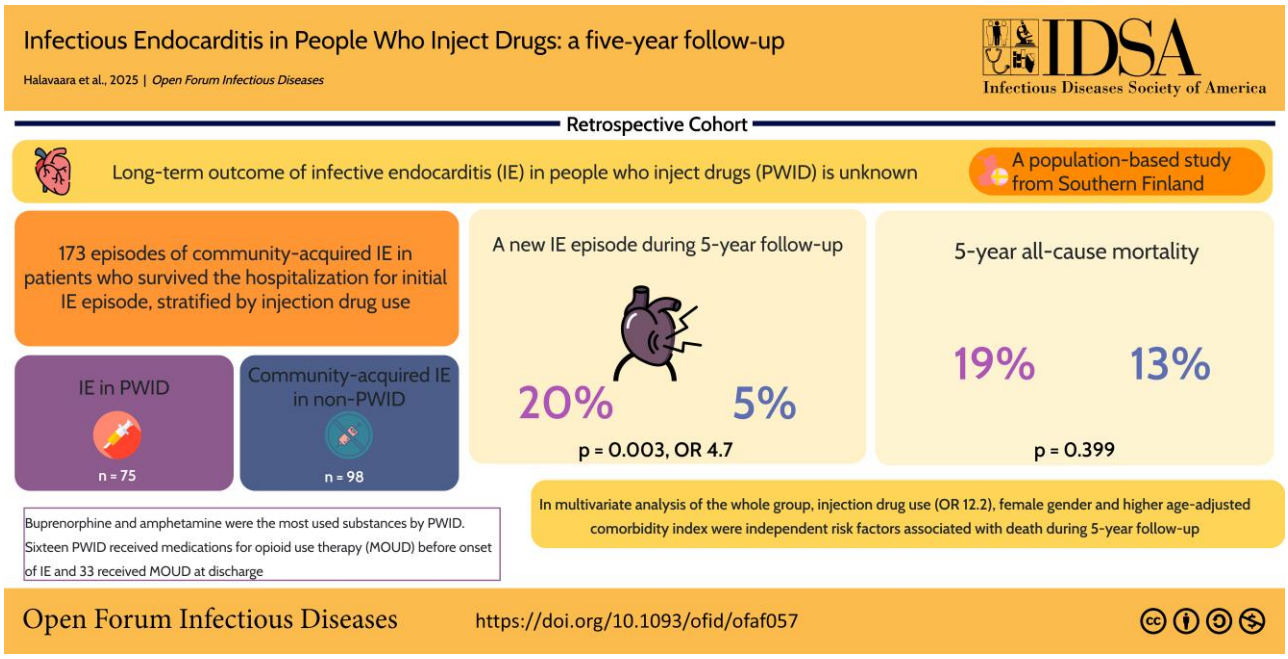
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/infectious-endocarditis-in-people-who-inject-drugs-a-five-year-follow-up-c38c9e96-25b5-4cca-b7dd-83a4e5e7fc36?utm_campaign=tidbitlinkshare&utm_source=lO

Keywords. addiction treatment; endocarditis outcome; infective endocarditis; intravenous drug use; persons who inject drugs.

Infective endocarditis (IE) in persons who inject drugs (PWID) is a distinct clinical entity with worrisome features: it affects young people with few, if any, comorbidities [1, 2]. Hallmarks of this infection are right-sided cardiac valve involvement, septic emboli to lungs, and *Staphylococcus aureus* as etiology [1–3]. In areas where intravenous drug use is prevalent, IE in PWID may constitute up to one-third of all IE cases, and its incidence is increasing [3–5].

Short-term prognosis of IE in PWID is better than that of IE in non-PWID [2]. Long-term prognosis, though, might be poorer. This is probably attributable to ongoing risk of infection due to continued use of intravenous drugs [6], compounded by the deleterious effects of the socioeconomic determinates of health. However, studies on the long-term outcome of IE in PWID have included a small number of cases, focused on surgically treated patients or used IE among non-PWID as a control group, in which case patients with health care–associated infection were also considered controls [7–9]. PWID with severe infection but without IE were used as a comparator group in a recent study [6]. Long-term survival was significantly lower in PWID with IE as compared with PWID with other infections. Moreover, population-based studies on long-term prognosis of PWID with IE are lacking.

As injection drug use is a major risk factor for IE, addiction referral has been linked to better outcome [1]. Additionally, IE in PWID is characterized by new IE episodes and relapse [2, 10]. A new IE episode might have different microbial etiology vs the initial episode [10].

In Finland, high-risk amphetamine and opioid use is prevalent. It is estimated that in 2017 there were 9100 to 13 000 problem users of these drugs in the study area, which is 1.16% to 1.66% of the whole population [11]. Incidence of problem drug use of amphetamine and opioids in Finland might be highest in Europe [12], and the incidence rose markedly during the study period [11, 13].

In the present population-based study, we report the 1- and 5-year survival of PWID with IE who survived the initial hospitalization of IE. We also report the rate of a new IE episode and its microbial etiology. For a comparator group, we included patients with community-acquired IE without a history of intravenous drug use. This is a novel approach. Finally, we describe the substances used by PWID and the nature of addiction treatment referral with these patients.

METHODS

Setting

This study included all adult patients (aged ≥18 years) who were diagnosed and treated for IE in Helsinki University Hospital and 2 Helsinki city hospitals from 2013 to 2017. Patients had to reside in the study area, which consisted of 6 municipalities in Southern Finland (including Helsinki) with an adult population of nearly 1 million.

Study Design and Participants

This was a retrospective population-based study. Patients were recognized from electronic medical records by *ICD-10* codes

for IE. Each case was then reviewed and included if it met the inclusion criteria and modified Duke criteria for possible or definite IE [14].

A total of 313 IE episodes and 292 patients were included. If a patient had a history of intravenous drug use within 3 months before onset of IE (self-reported), that episode was classified as intravenous drug use–related IE (n = 97). Of the remaining 216 episodes, 97 met the criteria for health care–associated IE and were classified accordingly. The remaining 119 were classified as community-acquired IE episodes. IE was defined as health care–associated IE according to following criteria: (1) onset of IE >48 hours after admission to the hospital or within 6 months after discharge from hospitalization for ≥2 days, (2) development of IE within 6 months after a significant invasive procedure, (3) extensive out-of-hospital contact with health care, or (4) residence in a nursing home or similar facility [3]. The detailed study protocol and inclusion criteria are presented in our previous publication [3].

For the present study, of the initial 97 intravenous drug use–related IE episodes arising from 84 patients, the first episode of IE for each patient during the study period (n = 84) was evaluated. Of these, 76 patients survived the initial episode of IE (ie, survived the initial hospitalization for IE and were discharged). One patient was excluded because of missing data. Thus, 75 patients were included in the present study. The comparator group consisted of patients with community-acquired IE (n = 119) who had their first IE episode during the study period (n = 115) and survived the initial IE episode (n = 98).

Patient Data and Definitions

Data on patient demographics and clinical details, including microbiology and imaging, were retrieved from medical and laboratory records. For the purposes of this new analysis, data were collected on substances used, receipt of medications for opioid use disorder (MOUD) before and after IE admission, and addiction treatment referral during hospitalization. In each case, only the main intravenously used drugs were reported (1 or 2, if reported by the patient), although it is acknowledged that most PWID may use multiple substances. Data were collected on HIV and hepatitis C virus infection (antibodies only). Age-adjusted Charlson Comorbidity Index was calculated for each patient [15].

A new IE episode was defined as an IE episode that was diagnosed >6 months after the end of the antibiotic treatment for the initial IE episode or if the causative microbe of IE was different; otherwise, an episode was classified as a relapse according to previous literature [1, 10, 16]. Problem drug use was defined as injecting drug use or long duration/regular use of opioids, cocaine, and/or amphetamines (or derivate) [11].

Patients were followed for at least 5 years after the diagnosis of IE by review of medical health records (including laboratory system and radiology records) and obituary register. Severe infections such as IE are treated solely in the study hospitals, which also have the only emergency departments in the study area. In the case of a new IE episode, patients would present and be treated in the study hospitals and thus captured. Also, the laboratory system is the same in all study hospitals; as such, a new bloodstream infection would be detected. In Finland, the Digital and Population Data Service Agency gathers basic information of all residents (eg, date of death if applicable). Data on mortality were retrieved from this database. Also, in Finland each resident has a unique 10-digit personal identification number, which allows a person's reliable identification from medical records from hospitals and other registries.

Patient Consent Statement

The research board at the Inflammation Center, Helsinki University Hospital, and city of Helsinki approved the study protocol. Due to the retrospective nature of the study, informed consent was waived.

Statistical Analysis

Categorical variables are presented by number and percentage. Continuous variables are presented as median and range. Differences between groups were compared with the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. Odds ratios (ORs) were calculated with 95% CIs, if applicable. Factors associated with 5-year survival were analyzed by multivariate logistic regression. Explanatory variables were included in the multivariable model if they gave significant *P* values in the univariate analysis. In addition, 3 variables (PWID, left-sided IE, and prosthetic valve) were included for their clinical relevance, regardless of their role in the univariate analysis. Any combination of multicollinear variables was not included in the multivariable model; in such situations, only 1 of the multicollinear variables was chosen for clinical relevance and previous literature. Survival data were analyzed with the Kaplan-Meir method and log-rank test. $P < .05$ was considered statistically significant. Statistical analyses were conducted with SPSS version 25.0 (IBM Corp).

RESULTS

In all, 173 patients with community-acquired IE were included in the study cohort. Of these, 75 were PWID with IE. The demographics, clinical features, and microbiology of these 75 cases are presented in Table 1 in comparison with 98 community-acquired IE episodes in non-PWID. Of note, as compared with patients with community-acquired IE without intravenous drug use, PWID with IE were younger; their age-adjusted Charlson Comorbidity Indexes were lower; and they more frequently had right-sided valve involvement, septic emboli outside the central nervous system, and *S aureus* infection.

Table 1. Patient Demographics, Risk Factors, and Clinical Characteristics of IE Episodes in PWID and Community-Acquired IE in Non-PWID

	IE in PWID (n = 75)	IE in Non-PWID (n = 98)	OR (95% CI)	*P* Value
Demographics and risk factors for IE				
Age, y, median (IQR)	35 (29–38)	62.5 (49–72)	…	**<.001**[a]
Male gender	47 (62.7)	75 (76.5)	0.52 (.27–1.00)	.064
Age-adjusted CCI, median (range)	0.0 (0–4)	2.0 (0–9)	…	**<.001**[a]
History of IE	9 (12.0)	4 (4.1)	3.21 (.95–10.85)	.078
Known cardiac risk factor for IE[b]	4 (5.3)	52 (53.1)	0.05 (.02–.15)	**<.001**
Location of IE[c]				
Prosthetic valve	3 (4.0)	11 (11.2)	0.33 (.09–1.23)	.098
Aortic valve alone	16 (21.3)	52 (53.1)	0.24 (.12–.47)	**<.001**
Mitral valve alone	14 (18.7)	44 (44.9)	0.28 (.14–.57)	**<.001**
Left-sided[d]	22 (29.3)	91 (92.9)	0.03 (.01–.08)	**<.001**
Tricuspid valve alone	53 (70.7)	7 (7.1)	31.32 (12.54–78.23)	**<.001**
Right-sided[e]	47 (62.7)	6 (6.1)	25.74 (9.96–66.50)	**<.001**
Bilateral	6 (8.0)	1 (1)	8.44 (.99–71.65)	**.044**
Microbial etiology of IE				
Staphylococcus aureus[f]	59 (78.7)	13 (13.3)	24.11 (10.79–53.86)	**<.001**
Viridans group streptococci	3 (4.0)	39 (39.8)	0.06 (.02–.21)	**<.001**
Enterococcus species	3 (4.0)	7 (7.1)	0.54 (.14–2.17)	.517
Complications of IE				
Cerebral complication[g]	4 (5.3)	15 (15.3)	0.31 (.10–.98)	**.049**
Septic emboli (other than cerebral)[h]	61 (81.3)	27 (27.6)	11.46 (5.52–23.79)	**<.001**
ICU admission[i]	10 (13.3)	2 (2)	7.39 (1.57–34.81)	**.005**
Heart failure needing MV/NMV	8 (10.7)	9 (9.2)	1.18 (.43–3.22)	.800
Operative treatment of IE	12 (16.0)	32 (32.7)	0.39 (.19–.83)	**.014**

Only patients who survived the initial IE episode are included. Data are presented as No. (%) unless otherwise indicated. Bold indicates $P < .05$. Odds ratio >1 indicates a higher likelihood of the outcome in PWID vs non-PWID.

Abbreviations: CCI, Charlson Comorbidity Index; CCU, cardiac care unit; ICU, intensive care unit; IE, infective endocarditis; MV, mechanical ventilation; NMV, nonmechanical ventilation; OR, odds ratio; PWID, people who inject drugs.

[a]Mann-Whitney *U* test.

[b]Valve disease, prosthetic valve, congenital heart condition, and hypertrophic cardiomyopathy.

[c]Based on imaging studies or clinical scenario.

[d]Affected valve is aortic valve, mitral valve, or both.

[e]Affected valve is tricuspid valve, pulmonary valve, or both.

[f]In all, 4 (5.6%) were methicillin-resistant and all in the PWID group.

[g]Cerebral complication means radiologically verified infarct, hemorrhage, or abscess.

[h]Includes infection foci related to IE.

[i]Postoperative ICU admission excluded.

Five patients had known HIV infection (4 PWID and 1 non-PWID). In all, 134 patients tested negative for HIV during hospitalization, and 34 were not tested at all (all non-PWID). Of the 5 patients with known HIV, 4 were undergoing antiretroviral therapy with CD4 counts >350 cells/mm^3, and 1 was without antiretroviral therapy (CD4 count, 184 cells/mm^3). Sixty-nine patients (39.9%) had hepatitis C antibodies, of which 68 were PWID; 47 (27.2%) tested negative and 57 (32.9%) were not tested.

Substances Used and Receipt of MOUD

Buprenorphine (31/75, 41%) and amphetamine or other stimulant (20/75, 27%) were the commonest substances used. Nineteen patients (25%) used buprenorphine (or heroin in 1 case and oxycodone in 1 case) and amphetamine or other stimulant. In 5 cases, the drug was not specified.

Sixteen patients (21%) received MOUD before the IE episode. Of these patients, 11 received methadone and 5 buprenorphine. During the hospitalization for IE, 65 patients (86.5%) underwent addiction specialist consultation and 10 patients refused. Seventeen patients started MOUD during hospitalization. Thus, 33 (44%) patients received MOUD at the time of discharge.

Comparison of First IE Episode With a New IE Episode

In all, 20 patients experienced a new IE episode during the follow-up of 5 years. Among patients, 20% (15/75) in the PWID IE group experienced a new IE episode as compared with 5.1% (5/98) in the non-PWID IE group ($P = .003$; OR, 4.65; 95% CI, 1.61–13.46). The survival analysis is shown in Figure 1. There was no apparent difference in the microbial etiology between the first and new IE episodes (Table 2).

Outcome

One-year all-cause mortality was 4.0% (3/75) in the PWID IE group and 4.1% (4/98) in the non-PWID IE group (OR, 0.98,

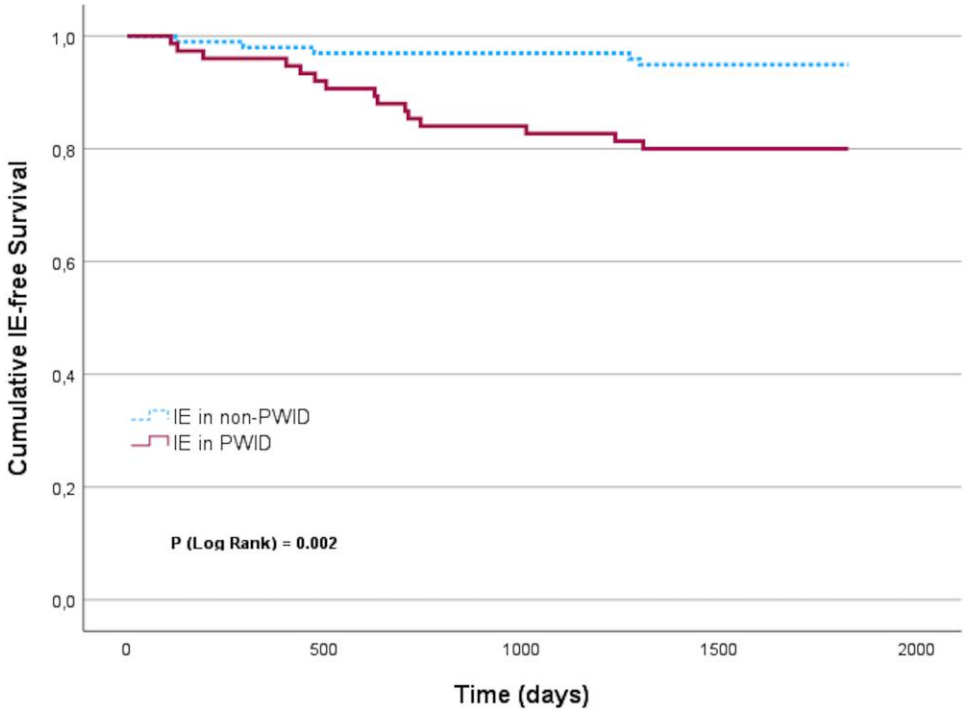


Figure 1. A Kaplan-Meier survival curve showing IE-free survival, stratified by injection drug use in patients with community-acquired IE (n = 173). Abbreviations: IE, infective endocarditis; PWID, people who inject drugs.

Table 2. Microbiological Etiology of the First-Ever IE Episode and the First New IE Episode in Patients Who Had a New IE Episode Within 5 Years (n = 18)

No. of Patients	First Episode[a]	Second Episode
IE in non-PWID		
1	MSSA	MSSA
2	VGS	VGS
1	VGS	MSSA
1	Unknown	VGS
IE in PWID		
4	MSSA	MSSA
1	VGS	VGS
2	VGS	MSSA
1	*E faecalis*	MRSA
1	*E faecalis*	MSSA
1	*E faecalis*	CoNS
1	MSSA	VGS
1	MSSA	Unknown
1	MSSA	*E faecalis*

Abbreviations: CoNS, coagulase-negative staphylococci; *E faecalis*, *Enterococcus faecalis*; IE, infective endocarditis; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; PWID, people who inject drugs; VGS, viridans group streptococci.

[a]Patients with a history of IE excluded (n = 2).

95% CI, .21–4.51). Five-year all-cause mortality was 18.7% (14/75) in the PWID IE group and 13.3% (13/98) in the non-PWID IE group (OR, 1.50; 95% CI, .66–3.42; $P = .399$). Five-year survival data are shown in Figure 2.

Risk Factors for 5-Year Mortality and a New IE Episode

In multivariate analysis, female gender (OR, 2.62; 95% CI, 1.01–6.82), Charlson Comorbidity Index >2, and injection drug use (OR, 12.15; 95% CI, 2.15–68.82) were independent risk factors for death during 5-year follow-up (Table 3).

DISCUSSION

In this study of 173 patients with community-acquired IE, 5-year survival was similar between IE in PWID and non-PWID. This finding highlights the poor long-term prognosis of PWID with IE, considering that PWID with IE are younger than non-PWID and have fewer comorbidities. Of note, even a trend toward a better 5-year prognosis was seen with non-PWID.

In those PWID with IE who survived the hospitalization for IE, 1-year survival was 96% and 5-year survival was 81%. When those who died during initial hospitalization (n = 9) are counted in, 1-year survival was 84% and 5-year survival was 69%. A study from Leeds, United Kingdom, based on 105 IE episodes in PWID between 2006 and 2016 reported a 1-year survival of 74% and 5-year survival of 58% [6]. A study examining 64 surgically treated PWID with IE reported 78% survival at 1 year and 47% at 5 years [9]. Unlike the aforementioned 2 studies [6, 9], our study was population based, so it analyzed IE cases from all difficulty levels. Considering that the

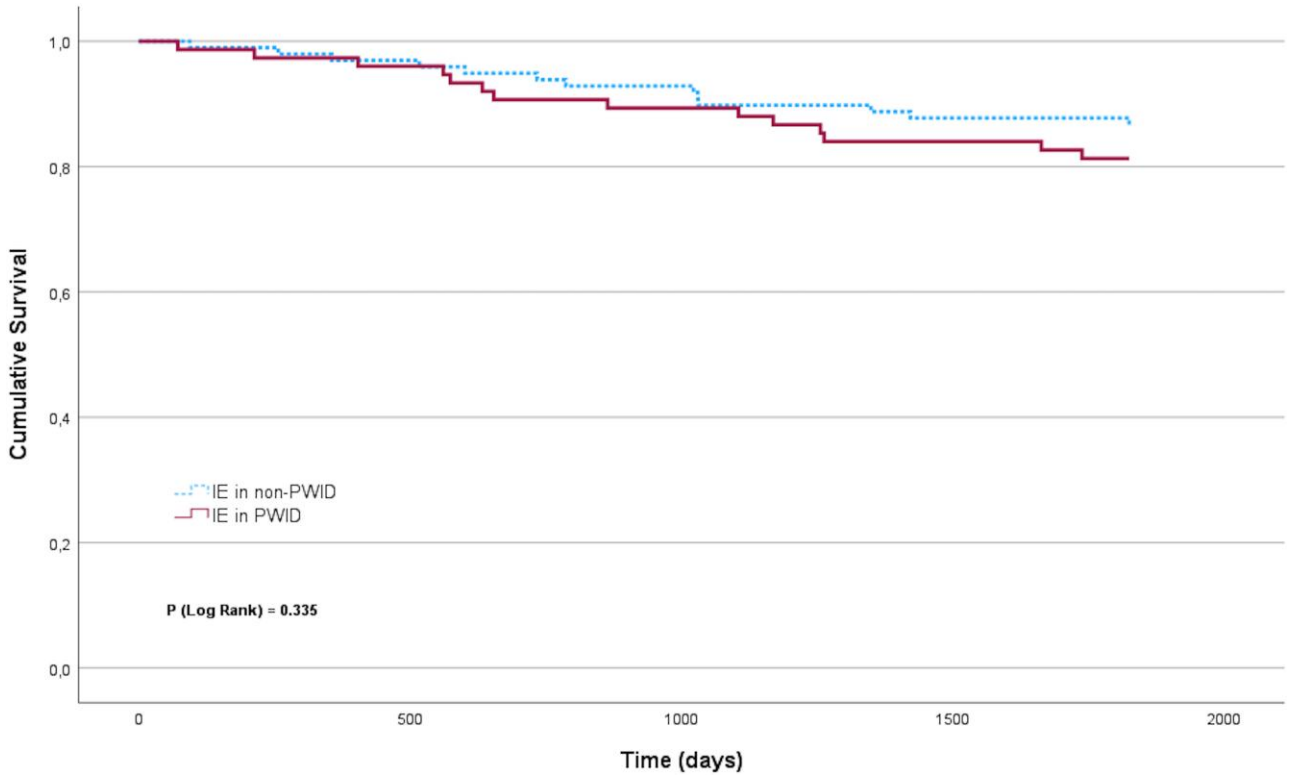


Figure 2. The 5-year survival of patients with community-acquired IE (n = 173) stratified by injection drug use. Abbreviations: IE, infective endocarditis; PWID, people who inject drugs.

Table 3. Univariate and Multivariate Analysis of 5-Year Mortality in Patients With Community-Acquired IE Who Survived the Initial IE Episode (N = 173)

	5-y Mortality			
	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Female gender	3.17 (1.37–7.36)	**.007**	2.62 (1.01–6.82)	**.048**
Charlson Comorbidity Index				
0	1 [Reference]			
1–2	0.41 (.11–1.53)	.183	0.94 (.22–4.08)	.939
3–4	2.21 (.67–7.30)	.193	7.04 (1.01–48.99)	**.049**
≥5	5.90 (1.88–18.5)	**.002**	27.45 (3.83–196.86)	**<.001**
Intravenous drug use	1.50 (.66–3.42)	.334	12.15 (2.15–68.82)	**.005**
History of previous IE	1.70 (.44–6.63)	.445	…	…
Left-sided IE	1.63 (.65–4.10)	.301	3.12 (.90–10.85)	.074
Prosthetic valve	2.37 (.68–8.18)	.174	0.85 (.19–3.83)	.828
Staphylococcus aureus as etiology of IE	0.66 (.28–1.56)	.344	…	…
Viridans group streptococci	0.34 (.10–1.20)	.095	…	…
Enterococci as etiology of IE	2.48 (.60–10.27)	.210	…	…
Stroke	1.02 (.28–3.76)	.981	…	…
ICU admission	1.09 (.23–5.27)	.917	…	…
Operative treatment	0.81 (.31–2.16)	.677	…	…

Bold indicates $P < .05$.

Abbreviations: ICU, intensive care unit; IE, infective endocarditis; OR, odds ratio.

median age of PWID was 35 years and only 69% survived the 5 years after IE, the lost years of life are staggering.

In a multivariate analysis of the whole group, injection drug use increased the odds of 5-year mortality 12 times vs community-acquired IE among non-PWID. PWID virtually lack other predisposing factors for IE. In our cohort, only 4% of PWID had a previously known cardiac risk factor for IE, as opposed to 52% in non-PWID. So, it is obvious that drug addiction and related injection drug use are the causes for PWID to develop IE and thus should be properly managed.

In our study, all PWID were offered addiction treatment consultation and 87% received it. In our setting, this included a telephone consultation and a possible visit from the addiction treatment service. PWID with opioid addiction were offered MOUD. Seventeen (23%) PWID who earlier did not receive MOUD received it during hospitalization and after discharge. In all, 44% of all PWID received MOUD after discharge. This is higher than in reports of IE in PWID from Ontario, Canada (17%) [1], and Massachusetts (24%) [17]. In addition, in a study of 102 PWID with IE, only 8% had a plan for MOUD [18]. Of note, in our study, a third of PWID reported mainly using amphetamine or another stimulant, and at present, there are no effective medications to treat the addiction caused by stimulants. Detailed data were not collected on other harm reduction measures (eg, instructions on sterile injection techniques), but these should be a priority in the treatment of IE in PWID [5].

Addiction medicine consultation has been shown to be an independent predictor of better short-term outcome in PWID with IE [1], and it has been associated with completion of antibiotic therapy and reduced risk of readmission in patients with serious infection from opioid use disorder [19]. However, a favorable effect of MOUD at the time of discharge is difficult to evaluate in terms of long-term prognosis, since MOUD seems to reduce mortality only during the months that it is used [17]. For these reasons, we did not analyze the impact of MOUD at discharge on 5-year survival.

Female gender was an independent predictor of worse 5-year prognosis (OR, 2.62) in an analysis of the whole study group. The mechanism by which women with IE have worse long-term outcome vs men is difficult to explain, and this has been shown previously [20].

Hospitalization for acute illness has been described as a reachable moment for PWID, for they otherwise do not readily seek health care contact [5]. This means not only addiction treatment referral but also a chance to test for blood-borne viruses. In this study, all PWID were tested for HIV and hepatitis C in health care services.

One-fifth of PWID with IE developed a new IE episode during 5-year follow-up. This was significantly more than non-PWID, and this finding is in line with previous reports [21]. However, in our study, these subsequent episodes were not caused more frequently by difficult-to-treat pathogens (eg, yeast and enterococci) as suggested in other studies [10, 21]. The reasons for this are unclear but may reflect the continued drug use following similar patterns in combination with overall low rates of resistant microbes in the study area and the resulting use of narrow-spectrum antimicrobials.

The strength of this study is its population-based design and detailed individual data on patients, including the intravenous drugs used. Yet, given the retrospective nature of this study, only the main 1 or 2 drugs injected were feasible to report. Most PWID may use multiple drugs, but a detailed history is seldom described in patients' medical records. Also, patients themselves are often reluctant to give detailed information on drug use. The limitations of this study are its retrospective design and lack of detailed history of adherence to MOUD and possible continued drug use in the years following discharge. Also, the numbers were too low to analyze the impact of receipt of MOUD on IE-free survival after initial IE. If a patient moved outside the study area after the IE episode, a possible repeat episode of IE would have been missed, but the number of such cases is estimated to be low.

We excluded microbial etiology from the multivariate model of 5-year prognosis due to collinearity, as 80% of PWID had *S aureus* as etiology. We tested the model by adding *S aureus* and viridans streptococci etiologies separately and in combination. In all these models, injection drug use remained a significant factor. Also, while *S aureus* was significantly associated with better outcome, this is most likely due to multicollinearity with PWID and could therefore be an unreliable finding. Additionally, when injection drug use was replaced for *S aureus* in the model, *S aureus* was not significant. In previous literature, *S aureus* has been associated with worse short-term prognosis (6 months) [22], but its impact on long-term prognosis is unknown. Given the relatively small number of cases in our study, these results should be interpreted as preliminary and so warrant confirmation in larger studies.

"I watched the needle take another man," sung Neil Young in his famous song in 1972. This study including community-acquired IE episodes reinforces the poor long-term prognosis of those patients who have injection drug use–associated IE. We agree with the American Heart Association that the need for adequate treatment and exploration of addiction, which is the major cause of IE in PWID, is crucial [23].

Notes

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Potential conflicts of interest. A. J. has received speaker honoraria from AstraZeneca, Shionogi, and Takeda and consultation fees from AstraZeneca, GlaxoSmithKline, and Nordic Infucare. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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