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1 **Title page**

2 **Long-term outcomes are poor in intravenous drug users**
3 **following infective endocarditis, even after surgery.**

4
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14
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19
20 **Key words:** Infective endocarditis, intravenous drug use, cardiac surgery.

21 **Running title:** Infective endocarditis and intravenous drug use.

22 **Word count:** 3042

23 **Number of tables:** 5

24 **Number of figures:** 3

25
26 **Summary:** Whilst early survival for people who inject drugs with infective endocarditis is good, long-
27 term survival is poor due to ongoing infection risk. Surgery conferred no long-term survival advantage,
28 so more efforts are needed to reduce re-infection risks for PWID.

30 **Abstract**

31 Words: 252

32

33 **Background**

34 Previous studies of outcomes in people who inject drugs (PWID) with infective
35 endocarditis (IE) have often been retrospective, had a small sample size, the duration
36 of follow-up has been short and limited to patients who were operated on.

37

38 **Methods**

39 PWID treated for IE between 01/01/2006 and 31/12/2016 were identified from a
40 prospectively collected database. PWID hospitalised with other infections acted as a
41 novel comparison group. Outcomes were all-cause mortality, cause of death, relapse,
42 recurrence and re-operation.

43

44 **Results**

45 There were 105 episodes of IE in 92 PWID and 112 episodes of other infections in
46 107 PWID in whom IE was suspected but rejected. Survival at 30 days for the IE group
47 was 85% and 30-day survival following surgery was 96%. The most common
48 pathogens were *Staphylococcus* spp. (60%) and *Streptococcus* spp. (30%). The
49 surgical intervention rate was 47%. Survival for the IE group at 1, 3, 5 and 10 years
50 was 74%, 63%, 58% and 44%, respectively. This was significantly lower compared
51 with the comparator group of other infections in PWID ($p=0.0002$). Mortality was higher
52 in patients who required surgery compared to those who did not (HR 1.8, 0.95-3.3).
53 The commonest cause of death was infection (66%), usually a further episode of IE
54 (55%).

55

56 **Conclusions**

57 Whilst early survival was good, long-term life-expectancy was low. This was
58 attributable to ongoing infection risk, rather than other factors known to affect
59 prognosis in PWID. Surgery conferred no long-term survival advantage. More efforts
60 are needed to reduce re-infection risk following an episode of IE in PWID.

61 **List of abbreviations**

62 IE – infective endocarditis

63 IVDU – intravenous drug use

64 PWID – people who inject drugs

65 UK – United Kingdom

66 qSOFA – quick Sepsis Related Organ Failure Assessment

67 mmHg – millimetres of mercury

68 spp. – species pluralis

69

70 **Manuscript text**

71 **Background**

72 The incidence of infective endocarditis (IE) is rising globally and in developed countries
73 acquired valve disease, valve prostheses, vascular instrumentation and intravenous
74 drug use (IVDU) are the leading causes [1-4]. IVDU is a predisposition for IE, with an
75 incidence 50-100 times higher in people who inject drugs (PWID) [5-7]. American and
76 European guidelines define heart failure, uncontrolled infection, large vegetation size
77 and embolization as indications for cardiac surgery, which is carried out in
78 approximately half of cases [7-9].

79

80 Previous studies of IE in PWID have been heterogenous. Most have been
81 retrospective, had a small size and limited to patients who underwent surgery [10-15].
82 Studies predating the development of the modified Duke criteria will have had less
83 accurate case identification than more recent series, potentially resulting in erroneous
84 reporting of the surgical intervention rate [10, 12, 14]. Lack of a comparator group [10,
85 16] or a control group of non-PWID patients [13, 14, 17] are additional limitations.
86 Although reported short-term survival in these studies is similar between the PWID
87 and non-PWID, the latter groups typically are older and have more comorbidities [12,
88 15]. Few studies have described the long-term outcomes for PWID with IE and none
89 have compared survival rates between those who were or were not operated on.

90

91 Important factors relevant to long-term outcomes and the timing of surgery in PWID,
92 that might be of less relevance in non-PWID patients, include non-adherence to
93 prescribed antimicrobial regimens and ongoing behaviours that increase the risk of re-
94 infection [10, 17]. The rate of re-operation in PWID is significantly higher than in non-

95 PWID [12, 15], which has prompted reflection and commentary on repeating surgery
96 in this patient group [18].

97

98 **Objectives**

99 We aimed to describe the characteristics, complications and long-term outcomes
100 following an episode of IE for a cohort of PWID presenting over a decade to the Leeds
101 Teaching Hospitals NHS Trust. The principle focus was the effect of surgery on long-
102 term outcomes. We also studied the re-infection rates and the causes of death and
103 how these findings might influence decision making regarding surgery for recurrent
104 infection. Finally, we compared outcomes in PWID who had confirmed IE (PWID-IE)
105 with PWID hospitalised for other infections (PWID-no-IE) during the same time period.
106 We hypothesised this would give a meaningful comparison group to determine the
107 extent to which an episode of IE affects survival beyond other factors known to
108 determine prognosis in PWID.

109

110 **Methods**

111 **Study design**

112 Observational cohort study, designed and reported using the STROBE statement [19].

113

114 **Ethics**

115 The study protocol was submitted to the Research and Innovation Department at our
116 institution. It was regarded as a service evaluation and therefore did not require
117 specific ethical approval or patient consent, providing that usual data protection was
118 in place. Only members of the clinical team had access to routinely collected data,
119 which were anonymised at the point of analysis.

120

121 **Funding**

122 No specific funding was used for the completion of this study.

123

124 **Setting**

125 This study was undertaken at the Leeds Teaching Hospitals NHS Trust which is a
126 tertiary referral centre for cardiology and cardiac surgery. Our centre comprises of two
127 large teaching hospitals with over two thousand inpatient beds and a catchment area
128 for referrals of over 3.5 million people of rural, urban and sub-urban demographics.

129

130 **Participants**

131 Consecutive patients aged 18 years or over reviewed between 01/01/2006 and
132 31/12/2016 were eligible to be included prospectively in a database designed for
133 service evaluation of IE management. Inclusion was dependent on the modified Duke
134 criteria [7]; we required episodes to be either Duke definite, or Duke possible and
135 treated for IE with IVDU within 90 days. PWID referred to the IE team for assessment
136 but were either Duke excluded or Duke possible and not treated for IE were regarded
137 as a comparator group.

138

139 **Variables and data sources**

140 The data for each patient were confirmed with reference to the written medical record
141 as well as local electronic data systems. The variables collected included patient
142 demographics, date of episode, severity of illness at presentation, affected
143 structure(s), microbiology and complications. These variables and IVDU status were
144 recorded routinely for all patients reviewed for suspected IE. Complications of IE were

145 defined as heart failure, emboli, failure of medical therapy or intracardiac abscess.
146 Those with indications for surgery were referred to the multidisciplinary heart team.
147 Decisions to operate were made by consensus and on an individual basis, with
148 indications for surgery defined by international guidelines. The timing, indication(s) for
149 and type of operation(s) were recorded. Emergency surgery was surgery within 24
150 hours, urgent within the index episode and elective following discharge from hospital.

151

152 **Outcomes**

153 The primary outcomes were all-cause mortality at 30-days following completion of
154 antimicrobial therapy, 30-days following surgery and at 1, 3, 5 and 10 years. Patients
155 were followed up until death or one year following study completion. Secondary
156 outcomes were IE-related mortality, relapse, recurrence and a second operation.
157 Outcome data were obtained from the Leeds Teaching Hospitals NHS Trust electronic
158 health record, which updates mortality events daily directly from the UK Office of
159 National Statistics (ONS) database. Dates and causes of death were confirmed from
160 the hospital medical records. In those without available electronic data, applications
161 were made to the local Coroner's office to obtain details of the recorded cause of
162 death.

163

164 **Statistical analysis**

165 A complete dataset was available for all variables except the severity of illness score
166 and cause of death. To assess the impact of missing values of the severity of illness
167 score, sensitivity analysis was performed using three regression models. In the first
168 model, we performed the analysis using complete cases only. For the second model

169 missing values were assigned zero points, and in the third they were assigned one
170 point.

171

172 Continuous variables are expressed as mean \pm standard deviation and discrete values
173 are presented as numbers and percentages. Unadjusted survival analysis is displayed
174 by Kaplan-Meier plot with survival differences determined by log-rank alongside 95%
175 confidence intervals for comparisons between: PWID-IE and PWID-no-IE, PWID
176 operated on and those managed conservative, and PWID who received mechanical
177 valve prostheses compared to bioprosthetic valves. A Cox regression model was
178 performed to determine the effects of surgery on all-cause mortality and was adjusted
179 for important covariables. The pre-specified confounding factors were age, sex,
180 severity of illness at presentation, left-sided IE and infection with *S. aureus*. In all
181 analyses a *p* value of <0.05 was regarded as statistically significant.

182

183 **Definitions**

184 An episode was considered to be a discrete inpatient period of treatment for infection.
185 Microbial cause of IE was determined by blood culture and/or by analysis of tissue
186 from excised valves obtained at operation. For the purpose of analysis, the aetiology
187 of infection was grouped as: *Staphylococcus aureus*, coagulase negative
188 staphylococci, beta-haemolytic streptococci, oral streptococci, *Streptococcus*
189 *anginosus* group, coliforms, enterococci, pseudomonads, *Candida*, 'other' and culture
190 negative.

191

192 Severity of illness was stratified by quick Sepsis Related Organ Failure Assessment
193 (qSOFA) score, which has been validated in prospective studies and shown to be of

194 greater prognostic accuracy than systemic inflammatory response syndrome or
195 severe sepsis criteria[20]. Heart failure was defined as the presence of clinically or
196 haemodynamically significant regurgitation, large vegetations causing haemodynamic
197 compromise or perforation.

198

199 The earliest episode during the study period was regarded as the index episode.
200 Relapse was IE caused by the same microorganism within a year, recurrence was re-
201 infection beyond one year, or infection with different microorganism. The start of an
202 episode was defined as the date of the first positive blood culture or echocardiogram.
203 The 30-day mortality and 30-day surgical mortality were any death within 30-days of
204 completion or therapy and operation respectively.

205

206 **Results**

207 **Participants**

208 199 PWID were assessed by the IE team. 105 episodes of IE occurred in 92 patients;
209 92 were Duke criteria definite and 13 Duke criteria possible. 112 episodes of other
210 infections occurred in 107 PWID not treated for IE; 111 were Duke excluded and 1
211 was Duke possible. The final diagnoses in PWID-no-IE were infected deep venous
212 thrombosis (41), skin or soft tissue infection (26), osteomyelitis (9), septic arthritis (6),
213 septic pulmonary emboli or lung abscess (5), central line infection (4), pneumonia (4),
214 urinary tract infection (2), pericarditis (2) and cerebral abscess (1). Whilst there was
215 no conclusive evidence of infection in 12 episodes.

216

217 **Patient demographics**

218 Of the 92 PWID-IE, 65 (71%) were male, the median age was 36 years with no
219 difference between male and females. The number of IE episodes varied considerably
220 from year-to-year with no clear trend. The median age increased throughout the study
221 period from 29 years to 42 years (Table 1). Of the 107 PWID-no-IE 69 were male
222 (64%) and the median age was 36 years.

223

224 **Microbiology**

225 The microorganisms causing IE were predominantly *Staphylococcus* species, whilst
226 *Streptococcus* species affected the majority of the remaining cases. There was a
227 similar distribution of infections in PWID-no-IE (table 2).

228

229 **Affected structures**

230 Left sided structures were involved in 72 (64%) episodes, whilst right sided
231 involvement occurred in 40 (36%) episodes; in 15 episodes more than one structure
232 was affected. Prosthetic valve infection accounted for 12 episodes. The mitral valve
233 was most commonly affected (44), followed by aortic (38), tricuspid (38) and
234 pulmonary (2). A pacemaker lead infection occurred in one patient and was treated by
235 extraction.

236

237 **Complications**

238 The most common complications were heart failure in 51 (49%) episodes, stroke in 16
239 (15%), pulmonary emboli in 20 (19%), splenic emboli in 11 (11%), other emboli in 8
240 (7%) episodes and aortic root abscess in 2 (2%) episodes. Thrombo-embolism to other
241 sites included renal, mesenteric, upper and lower limb arteries. There was one
242 instance of endophthalmitis.

243

244 **Surgery**

245 Surgery was undertaken in 49 (47%) episodes for 48 patients. There were no
246 significant differences in age, sex, *S. aureus* infection or severity of illness score
247 between those requiring surgery and those who did not, but operated patients were
248 significantly more likely to have left sided infection (Table 1). Heart failure was the
249 primary indication for surgery in 33 episodes and a secondary indication in four (total
250 76%). Aortic root abscess was the indication in one episode (1%), embolization being
251 the primary indication in 14 and secondary indication in 15 episodes (total 28%) and
252 infection with fungi was the indication for one (1%).

253

254 Emergent surgery was performed in five episodes (10%). Surgery was performed on
255 an urgently in 42 episodes (86%) and electively following discharge for two patients
256 (4%). Bioprosthetic valve replacement for left-sided IE was the commonest surgical
257 procedure (Table 3). There was one attempt at pulmonary valve replacement which
258 was abandoned on technical grounds owing to inflammatory adhesions. Combined
259 surgical procedures were undertaken for nine patients. During the study period only
260 one patient underwent repeat surgery due to late recurrence of *S. epidermidis* affecting
261 a bioprosthetic mitral valve.

262

263 Major complications occurred in 29 episodes in which surgery was not undertaken, in
264 21 episodes there was no class I indication for surgery. In eight episodes there was a
265 class I indication, however patients were too unwell to undergo an operation and did
266 not survive.

267

268 **Relapses and recurrences**

269 Relapse occurred in three (3%) patients, one patient had two episodes of relapse, and
270 all were caused by early re-infection with *S. aureus*. Recurrence occurred in 12 (13%)
271 patients, one of whom had two episodes of recurrence. In sub-group analysis of those
272 with recurrence, eight (75%) were not alive at follow-up, three deaths occurred within
273 30 days, and IE-related mortality was documented in 6 cases.

274

275 **Survival**

276 The 30-day mortality was 16 (15%) and the 30-day surgical mortality was 4 (8.5%).
277 During a median follow-up of 3.4 years, there were a total of 42 deaths (46%). The
278 long-term survival for PWID-IE and PWID-no-IE are shown in table 4. In Kaplan-Meier
279 analysis, survival was significantly lower in PWID-IE compared to PWID-no-IE
280 ($p=0.0002$) (Figure 1). There was no statistically significant difference in survival in the
281 operated group compared to the non-operated group ($p=0.067$) (Figure 2), and this
282 was true when adjusted for the pre-specified covariates (Table 5) and when surgery
283 was analysed as a time-dependent variable (Supplementary table 1). There was no
284 association between choice of bioprosthetic or mechanical valve replacement and
285 survival ($p=0.12$) (Figure 3).

286

287 Additionally, a large proportion of both groups failed to reach predicted life-
288 expectancy. Taking the median ages of the males (36 years) and females (34 years)
289 in this study, then the expected life expectancies for each sex are 73.7 years and 74.2
290 years, respectively referring to data published by the UK ONS [21] (Supplementary
291 table 2).

292

293 **Causes of death**

294 Medical certificates for cause of death were available for 38 patients (90%). 21 deaths
295 were reported to be due to an episode of IE. Drug overdose was the recorded cause
296 of death for six patients, and in four patients death was due to another infection. In two
297 patients cardiac failure was the documented cause of death and for one patient the
298 cause of death was unascertained.

299

300 **Conclusions**

301 The principle finding of this study was that a low 30-day mortality relative to IE mortality
302 in general did not translate into favourable long-term outcomes in a cohort of PWID-
303 IE. By analysis of predicted survival from the ONS it is evident that the total number of
304 lost years-of-life is very high.

305

306 Our findings reinforce earlier reports of high early survival followed by poor long-term
307 outcomes in PWID-IE. In a series of 280 PWID-IE patients, Arbulu et al. reported a
308 mortality rate of 21% during an unspecified period of follow-up[16]. In a cohort of 29
309 PWID undergoing surgery for IE, Osterdal et al. reported death in 13 (45%) patients
310 during a median follow-up period of 22 (0-84) months, with reported 2 and 5-year
311 survival rates of 79 and 59%, respectively[10]. Rabkin et al. reported survival in the
312 PWID group of 91%, 78%, 47% and 41% at 30 days, 1-year, 5-years and 10-years[14].
313 In a comparison of non-PWID patients with PWID patients, Thalme et al. reported that
314 all five PWID who underwent cardiac surgery had died after 3.3 years[13].

315

316 All patients in our cohort who underwent surgery had a class I indication and some
317 had multiple indications, so there is no suggestion from this work that surgery could

318 have been withheld from these patients. Surgical correction of heart failure caused by
319 significantly regurgitant heart valves in the setting of IE is recommended on prognostic
320 grounds in appropriately selected patients[22]. The lack of a survival benefit in those
321 PWID that underwent surgery may be due to differences in disease severity; the
322 operated cohort had worse valvular dysfunction, heart failure or had uncontrolled
323 infection. However, in the absence of trials, a survival benefit of surgery in this group
324 should not be assumed. Our cause-of-death analysis provides possible explanations
325 for the high mortality, whichever treatment pathway is chosen with the unique finding
326 that death in half the patients was caused by a further episode of IE. Although recent
327 data have supported the concept of survival benefit from surgery, their cohort had
328 more right-sided disease, and a lower surgical intervention rate than in our series [23].
329

330 All patients were offered support by the local drug dependency service. This
331 comprised a visit from a designated key worker and where indicated, prescription of
332 medications for opioid use disorder. Despite this, similar to other reports, our cohort
333 had a high rate of return to drug use and re-infection, and only 44% of patients were
334 alive at 10 years. Arbulu et al. reported that all of the 23 late deaths they observed
335 were associated with continued IVDU, whereas all 70 patients who ceased injecting
336 drugs survived[16]. Rabkin et al. reported eight cases of re-infection in the PWID sub-
337 group, which was higher than the non-PWID group (13% compared to 2%). Osterdal
338 et al. found on-going IVDU rates of 70% and 44% in patients undergoing a first or
339 second operation, respectively[10]. Kim et al. compared PWID with non-PWID and
340 found that despite a similar long-term survival, rate of re-infection were much higher
341 in PWID (36% compared to 4%, $p<0.001$)[12]. In the largest contemporary analysis

342 of PWID with IE, Rodger et al. demonstrated that drug addiction services were one
343 factor which helped improve outcomes[23].

344

345 Our comparator group (PWID-no-IE) had better survival than PWID-IE (Figure 1),
346 implying that cardiac infection has a negative impact on survival in PWID beyond
347 infection elsewhere. It seems likely that damaged native heart valves, or indwelling
348 prosthetic material poses increased risk of re-infection in the setting of continued
349 IVDU. None of the international guidelines make specific recommendations for cardiac
350 surgery in PWID. In clinical practice, we often encounter the difficult issue that the
351 threshold for operation (and especially repeat operations) could be higher in PWID-IE
352 than non-PWID in whom the re-infection rate is lower, however we do not feel that this
353 work supports withholding surgery from PWID. Survival was not affected by the choice
354 or mechanical or bioprosthetic valve, although the numbers at risk were small. The
355 lack of requirement for anticoagulation is relevant in this patient group whose younger
356 age would usually favour the choice of more reliable mechanical valve replacements.

357

358 **Study limitations**

359 We prospectively collected data on factors that are known to affect outcomes in IE but
360 it is likely that other confounding factors were present but unmeasured. Another
361 limitation of this study is the single centre setting, meaning the generalisability is
362 uncertain. However, our study represents a large contemporary case series of IVDU
363 related IE, reports outcomes from all affected valves, and includes patients managed
364 both medically and surgically. The preponderance of left-sided disease may reflect
365 inclusion bias, as a cardiac surgery referral centre will receive more patients with left-

366 sided infection complicated by heart failure or embolic risk, but is consistent with other
367 recent studies [10, 12, 14]. The high rate of IE-related mortality suggests that the
368 relapse and recurrence rates reported here may have underestimated the rate of re-
369 infection. A major limitation of our project was that we did not collect detailed data on
370 specific drug addiction services offered to PWID or their uptake.

371

372 **Key findings**

373 Following an episode of IE, the long-term survival for patients with predisposing IVDU
374 was poor. Whilst surgery can redress haemodynamic and embolic complications, it is
375 only a part of the holistic approach necessary to manage this challenging patient
376 group. A review of the approach to surgical treatment in these individuals and the
377 support and harm reduction input these patients receive may be necessary especially
378 in those who persist with IVDU and develop re-infection, requiring a second operation
379 [24].

380 **Notes**

381

382 **Declaration of interests**

383 JS participates in research with funding from Pfizer and Merck Sharpe and Dohme.

384 KKW receives consulting fees from Medtronic, Bayer and Novartis; receives speaking

385 fees from Medtronic, Bayer, Novartis, Napp and Abbott; and holds an unrestricted

386 research grant from Medtronic. There are no conflict of interests to declare for the

387 other authors.

388

389 **Authorship**

390 SS, WB and JS researched the topic and devised the study.

391 JS, SS, WB and RG collected the data and undertook primary statistical analysis.

392 SS and WB produced the first draft of the manuscript.

393 All other co-authors contributed to manuscript preparation.

394

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400 team for their assistance with patients in the present study.

401 The research took place at the Leeds Teaching Hospitals NHS Trust and the Leeds

402 NIHR Clinical Research Facility.

403

404 **Table 1.**

405 Title: Characteristics of patients with infective endocarditis stratified by surgery.

406 Caption: Baseline characteristics are similar in those operated and non-operated with
 407 the exception of left-sided infection.

408

Characteristic	All patients	Not operated	Operated	P-
	n = 92	n=47	n=45	value
Age (years), mean				
(sd)	36.7 (8.4)	36.1 (8.7)	37.4 (8.2)	0.49
Male	65 (71)	33 (70)	32 (71)	1.0
S. aureus	53 (58)	30 (64)	23 (51)	0.31
Side				
Left-side	49 (53)	20 (43)	29 (64)	
Right-side	30 (33)	24 (51)	6 (13)	<0.001
Both	13 (14)	3 (6)	10 (22)	
qSOFA >= 2	12 (16)	7 (18)	5 (14)	0.87

409

410

411 **Table 2.**

412 Title: Microorganisms causing infection in PWID-IE and PWID-no-IE

413 Caption: *Staphylococcus* and *Streptococcus* species caused the majority of

414 infections in PWID.

415

Microorganisms	PWID-IE (n)	PWID-no-IE (n)
<i>S. aureus</i>	63	39
Coagulase-negative <i>Staphylococcus</i>	2	3
Beta-haemolytic <i>Streptococci</i>	19	16
Oral <i>Streptococci</i>	9	6
<i>Streptococcus anginosus</i>	3	6
<i>Enterococcus</i> spp.	8	2
Coliforms	0	3
<i>Candida</i> spp.	2	0
Pseudomonads	1	1
Other	1	3
Culture negative	7	41

416

417

418 **Table 3.**

419 Title: Surgical procedures by type and affected structure

420 Caption: Bioprosthetic valve replacement for left-sided IE was the commonest surgical
421 procedure.

422

Surgical procedure	n
Aortic valve replacement	24
Bioprosthetic	18
Mechanical	6
Mitral valve replacement	19
Bioprosthetic	11
Mechanical	9
Tricuspid valve replacement	8
Pulmonary valve replacement	1
Aortic valve repair	1
Mitral valve repair	5

423

424

425 **Table 4.**

426 Title: Overall survival and survival in patients stratified by surgery with 95% confidence
 427 intervals.

428 Caption: Survival was reduced in the operated group compared to the non-operated
 429 group. Survival was reduced in patients with endocarditis compared to controls.

430

Kaplan-Meier survival rate (95% CI)				
	Endocarditis	Endocarditis operated	Endocarditis not operated	Controls
1 year	73.9 (65.5-83.5)	68.9 (56.6-83.8)	78.7 (67.9-91.3)	91.0 (85.6-96.8)
3 years	62.7 (53.3-73.8)	53.7 (40.5-71.1)	71.5 (59.4-86.0)	86.4 (79.8-93.6)
5 years	58.3 (48.6-70.0)	47.9 (34.7-66.1)	68.5 (55.9-83.9)	83.5 (76.1-91.6)
10 years	43.8 (32.0-59.9)	33.0 (18.4-59.1)	53.2 (36.8-77.1)	70.0 (59.6-82.3)

431

432

433

434 **Table 5.**

435 Title: Cox regression analysis for the association between operation and survival
 436 adjusted for important clinical covariables.

437 Caption: In univariate analysis and when adjusted for important clinical covariables,
 438 surgery is not associated with a favourable prognosis.

439

	Mortality, hazard ratio (95% CI)			
	Univariable	Multivariable	Multivariable	Multivariable
	model	model 1*	model 2*	model 3*
	n=92	n=73	n=92	n=92
Surgery (Yes vs No)	1.8 (0.95-3.3)	1.4 (0.68-2.7)	1.3 (0.68-2.6)	1.7 (0.75-3.8)
Age		1.0 (0.96-1.1)	1.0 (0.98-1.1)	1.1 (1.0-1.1)
Sex (Male vs Female)		0.98 (0.48-2.0)	1.0 (0.50-2.1)	0.67 (0.30-1.5)
<i>S. aureus</i> (Yes vs No)		0.73 (0.38-1.4)	0.81 (0.43-1.5)	0.43 (0.20-1.9)
Side				
Left-side		1	1	1
Right-side		0.44 (0.18-1.1)	0.46 (0.19-1.1)	0.52 (0.19-1.4)
Both		0.67 (0.24-1.8)	0.70 (0.25-1.9)	0.20 (0.04-0.95)
qSOFA				
<2		1	1	1
>=2		1.9 (0.74-5.0)	1.5 (0.73-2.9)	2.7 (0.95-7.4)

Model 1: complete case for qSOFA

Model 2: altered mentation, systolic blood pressure ≤ 100 , respiratory rate ≥ 22 were set to 0 if unknown

Model 3: altered mentation, systolic blood pressure ≤ 100 , respiratory rate ≥ 22 were set to 1 if unknown

440

441

442 **Supplementary table 1.**

443 Title: Cox regression analysis for the association between operation and survival
 444 adjusted for important clinical covariables. Surgery was coded as time-dependent
 445 variable where the date of operation was taken into account in the Cox model.

446 Caption: Survival was not associated with operation in univariate or multivariable
 447 analysis.

448

	Mortality, hazard ratio (95% CI)			
	Univariable	Multivariable	Multivariable	Multivariable
	model	model 1*	model 2*	model 3*
	n=92	n=73	n=92	n=92
Surgery (Yes vs No)	1.64 (0.91-3.01)	1.29 (0.61-2.65)	1.22 (0.59-2.32)	1.58 (0.71-3.47)
Age		1.0 (0.98-1.04)	1.0 (0.98-1.05)	1.04 (1.0-1.08)
Sex (Male vs Female)		1.08 (0.49-1.67)	1.09 (0.51-1.67)	0.65 (0.31-1.29)
<i>S. aureus</i> (Yes vs No)		0.77 (0.24-1.30)	0.82 (0.31-1.33)	0.46 (0.22-1.12)
Side				
Left-side		1	1	1
Right-side		0.31 (0.18-1.04)	0.31 (0.19-1.03)	0.30 (0.11-1.12)
Both		0.63 (0.24-1.46)	0.64 (0.23-1.45)	0.15 (0.01-1.63)
qSOFA				
<2		1	1	1
>=2		1.63 (0.88-2.39)	1.50 (0.95-2.04)	2.21 (1.42-2.99)

Model 1: complete case for qSOFA

Model 2: altered mentation, systolic blood pressure ≤ 100 , respiratory rate ≥ 22 were set to 0 if unknown

Model 3: altered mentation, systolic blood pressure ≤ 100 , respiratory rate ≥ 22 were set to 1 if unknown

449

450

451 **Supplementary table 2.**

452 Title: Life expectancy with 95% confidence interval for IVDU patients with IE stratified
 453 by surgery and sex.

454 Caption: The life expectancy of a healthy 36 year-old male is an additional 44.3 years
 455 and of a healthy 34 year-old female is 49.6 years. In comparison, the life expectancy
 456 for IVDU patients following an episode of endocarditis is substantially less, particularly
 457 in the operated group.

458

		Life expectancy after treatment (years)		
		10-year mortality rate (%)	for a 36-year old	
			male	female
Male	Surgery	80 (68,92)	6.2 (3.9, 8.8)	-
	No surgery	49 (43,55)	14.4 (12.4,16.9)	-
	Overall	60 (52,68)	10.7 (8.7,13.4)	-
Female	Surgery	57 (46,67)	-	11.8 (9.1,15.7)
	No surgery	36 (30,42)	-	20.6 (17.5,24.1)
	Overall	46 (38,54)	-	15.6 (12.7,19.4)

459

460

461 **Figure titles and legends**

462

463 **Figure 1.**

464 Title: Kaplan-Meier plot of the survival of PWID in cases with confirmed infective
465 endocarditis compared to PWID with other infections.

466 Caption: Survival was significantly reduced following an episode of infective
467 endocarditis compared to PWID with other infections ($p=0.0002$).

468

469 **Figure 2.**

470 Title: Kaplan-Meier plot of the survival of PWID in cases with confirmed infective
471 endocarditis, stratified by operated or not operated.

472 Caption: There was a trend towards reduced survival in the operated group ($p=0.067$)

473

474 **Figure 3.**

475 Title: Kaplan-Meier plot of the survival following surgery for infective endocarditis in
476 those receiving bioprosthetic or mechanical valve replacements.

477 Caption: There is no significant difference in survival between those receiving
478 mechanical or bioprosthetic valve replacement.

479

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