Original research

Clinical profile and outcome of recurrent infective endocarditis

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ABSTRACT

Aims Purpose of this study is to compare the clinical course and outcome of patients with recurrent versus first-episode infective endocarditis (IE).

Methods Patients with recurrent and first-episode IE enrolled in the EUROpean ENDOcarditis (EURO-ENDO) registry including 156 centres were identified and compared using propensity score matching. Recurrent IE was classified as relapse when IE occurred ≤6 months after a previous episode or reinfection when IE occurred >6 months after the prior episode.

Results 3106 patients were enrolled: 2839 (91.4%) patients with first-episode IE (mean age 59.4 (±18.1); 68.3% male) and 267 (8.6%) patients with recurrent IE (mean age 58.1 (±17.7); 74.9% male). Among patients with recurrent IE, 13.2% were intravenous drug users (IVDUs), 66.4% had a repaired or replaced valve with the tricuspid valve being more frequently involved compared with patients with first-episode IE (20.3% vs 14.1%; p=0.012). In patients with a first episode of IE, the aortic valve was more frequently involved (45.6% vs 39.5%; p=0.061). Recurrent relapse and reinfection were 20.6% and 79.4%, respectively. *Staphylococcus aureus* was the microorganism most frequently observed in both groups (p=0.207). There were no differences in in-hospital and post-hospitalisation mortality between recurrent and first-episode IE. In patients with recurrent IE, in-hospital mortality was higher in IVDU patients. Independent predictors of poorer in-hospital and 1-year outcome, including the occurrence of cardiogenic and septic shock, valvular disease severity and failure to undertake surgery when indicated, were similar for recurrent and first-episode IE.

Conclusions In-hospital and 1-year mortality was similar in patients with recurrent and first-episode IE who shared similar predictors of poor outcome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Infective endocarditis (IE) is a disease still burdened by high morbidity and mortality despite improvement in its management, and its recurrence is associated with a worse prognosis.

⇒ Numerous studies have investigated clinical and echocardiographic characteristics of IE recurrence with conflicting results.

WHAT THIS STUDY ADDS

⇒ This study investigated a large population of patients with recurrent IE (n=267) compared with patients with a first episode of IE (n=2839), evaluating clinical aspects, in-hospital and post-hospitalisation outcome.

⇒ In both groups, independent predictors of poorer in-hospital and 1-year outcome were the occurrence of cardiogenic and septic shock, valvular disease severity and failure to undertake surgery when indicated.

⇒ Among patients with recurrent IE, in-hospital mortality was higher in those with reinfection within 6 months of hospitalisation (relapse) and in intravenous drug users.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Recurrent IE per se is not associated with an increased in-hospital and post-hospitalisation mortality compared with a first episode of IE; however, more attention should be paid in both patient subsets to the occurrence of in-hospital complications that may affect prognosis.

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INTRODUCTION

Infective endocarditis (IE) is still burdened by high morbidity and mortality despite improvements in diagnostic and therapeutic strategies.[1] The EURO-ENDO study is a large multicentre registry, which enrolled 3116 patients with IE from the European Society of Cardiology (ESC) and non-ESC-affiliated countries with detailed epidemiological and microbiological findings and clinical course during hospitalisation and at 1-year follow-up.[2] The recently published results of EURO-ENDO have demonstrated that patients affected by IE generally had multiple comorbidities, and absence of surgery when indicated was associated with a worse outcome.[3] Different studies have investigated comparison among recurrent and first IE episode with conflicting results.[4–7]

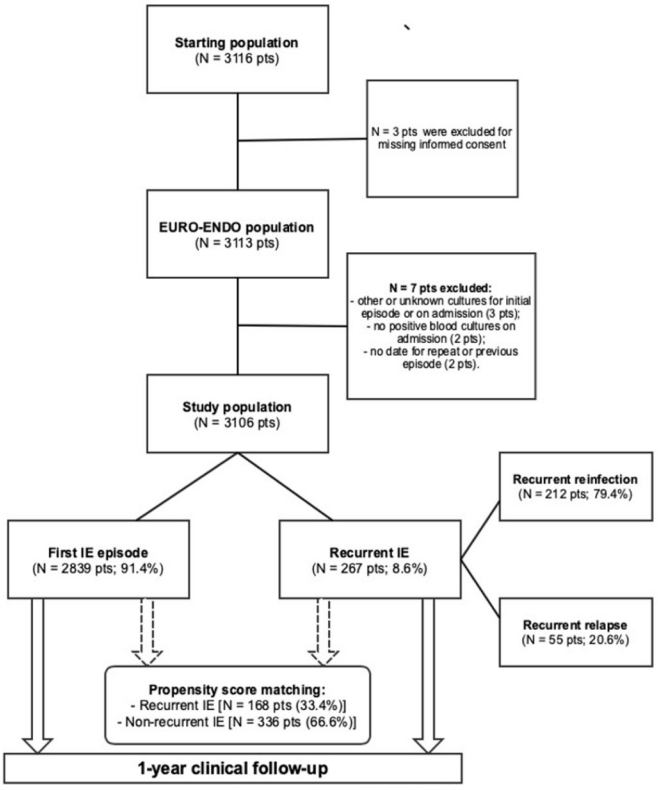

Figure 1 Flow chart of study design. IE, infective endocarditis.

The aim of this study was (i) to assess the clinical features and outcome of patients with recurrent IE in comparison with patients with a first episode of IE and (ii) to evaluate the determinants of in-hospital and follow-up mortality using propensity-matched groups for comparison.

METHODS

From 1 January 2016 to 31 March 2018, all centres participating in the EURO-ENDO registry included consecutive patients aged >18 years over a 1-year follow-up period with a diagnosis of definite IE (or possible IE, considered and treated as IE) based on the 2015 ESC IE diagnostic criteria.[2 8] The total duration of participation of each centre was 2 years, with end of follow-up in March 2019.

After informed consent, data were collected at inclusion and during hospitalisation. Patients were not involved in the design, conduct, reporting or dissemination plans of our research. The study was approved by each local Ethic Committee.

Patients with no previous admission for IE were defined as experiencing first-episode IE. Recurrent IE was further classified as relapse if the episode of IE occurred ≤6 months after a previous episode and caused by the same microorganism or reinfection if the episode occurred >6 months or was caused by a different microorganism.[9] When a microorganism was not identified, the event was considered reinfection or relapse according to the time elapsed between previous and current IE episode (figure 1). An additional analysis was explored among patients with first-episode IE and recurrent IE, excluding patients with negative blood culture (online supplemental table 1A-C).

Data about history, demographics, clinical, biological, microbiological, imaging diagnostic findings, medical and surgical treatment, complications on therapy and in-hospital death were collected for each group. Complications and mortality at 1-year follow-up were also analysed. A subanalysis involving intravenous drug users (IVDUs) was performed to evaluate the characteristics of IE recurrence in these patients. Furthermore, an additional analysis was performed in patients with recurrent IE with prosthetic versus native valve (online supplemental table 2A–D).

Data management and statistical analysis

Continuous variables were expressed as mean±SD, or median and IQR. Comparisons among recurrent versus first-episode IE and recurrent relapse versus recurrent reinfection were performed using Kruskal-Wallis test. Categorical variables were expressed as frequency and percentages. Among-group 2×2 comparisons were made using Pearson's χ^2 test or Fisher's exact test if any expected cell count was <5. Plots of the Kaplan-Meier curves for all-cause mortality and log-rank test were performed. All epidemiological, clinical, microbiological, echocardiographic variables were tested with univariable Cox regression analysis for the association with the risk of mortality during the hospitalisation and at follow-up. Variables with p<0.10 were entered in a multivariable adjusted Cox proportional hazard model with a backward selection procedure and a significance level of p≤0.05. Goodness of fit and concordance were calculated to verify the adequacy of the models.

A propensity-based matching approach was used to create patient samples with recurrent and non-recurrent IE with similar characteristics (online supplemental table 3). The propensity score was calculated using multivariable logistic regression including age, sex, endocarditis location (aortic, mitral, tricuspid, pulmonary, intracardiac device-related), prosthesis or valve repair, intravenous drug dependency, heart failure, diabetes mellitus, left ventricular ejection fraction, presence of *Staphylococcus aureus* IE, enterococci, chronic renal failure, vegetation presence on first echo examination at admission, abscess, pseudoaneurysm or severe regurgitation or valve stenosis on first echo examination at admission, arterial hypertension, chronic obstructive pulmonary disease/asthma, days from symptom onset to hospitalisation, embolic events during hospitalisation, haemorrhagic stroke.

A 2:1 optimal matching algorithm without replacement was used, where patients with recurrent IE were matched to the closest patient with non-recurrent IE within a range of 0.20 SD of the logit of the estimated propensity score. The success of propensity score matching was assessed by checking standardised differences between groups before and after matching, that is, the absolute difference in sample means divided by an estimate of the pooled SD of the variable, expressed as a percentage (online supplemental material, pp. 33–97). Balancing was considered as successful if the standardised differences were <10% for variables used for propensity score development. Thirty-day and 1-year mortality rates were compared using multivariable adjusted Cox proportional hazard model with a backward selection procedure and a significance level of p≤0.05, stratifying on matched pairs.

A two-sided p value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 3113 patients with IE from 156 hospitals in 40 countries were included in the EURO-ENDO registry (7 patients were excluded from the initial population), of whom 267 (8.6%) had recurrent IE and 2839 (91.4%) had a first episode of IE (figure 1). Among recurrent IE, reinfections and relapses were

observed in 212 (79.4%) and 55 (20.6%) patients, respectively (Table 1). Demographic, clinical, echocardiographic and microbiological data of the study population are reported in table 1.

Recurrent versus first-episode infective endocarditis

Patients with a first episode of IE and those with recurrent IE did not differ in terms of age and Charlson Comorbidity Index. In patients with recurrent IE, IE most frequently involved the prosthetic/repaired valve (66.4%) and occurred in IVDUs (13.2%) (table 1 and online supplemental table 2). The median days from symptom onset to hospitalisation were longer in patients with first-episode IE. There were no differences between groups in New York Heart Association (NYHA) class at admission but patients with a first episode of IE had higher N-terminal pro B-type natriuretic peptide (NT-proBNP). *S. aureus* was the most frequently isolated microorganism in both groups, followed by enterococci and viridans group streptococci. On echocardiography, the aortic valve was more often involved in patients with a first episode of IE. Conversely, the tricuspid valve was more often involved in patients with recurrent IE showing most often right ventricular dysfunction. In both groups, the major complications while on therapy were embolic events, which occurred in 22.1% and 20.5% of patients with recurrent and first-episode IE, respectively (table 2).

Cardiac surgery was less frequently performed in patients with recurrent IE than in those with a first episode of IE (64.8% vs 74.8%; p=0.012). In both groups, the main indication for surgery was due to complications related to cardiac infection, followed by haemodynamic instability and embolic events. In-hospital death occurred in 48 (18.0%) patients with recurrent IE and in 481 (16.9%) patients with a first episode of IE. Among patients with recurrent IE, there were no differences in in-hospital and 1-year mortality among those with a native or prosthetic/repaired valve (online supplemental table 2B-C).

Infective endocarditis reinfection versus relapse

The incidence of recurrent IE was about 8.9% and 8.2% in ESC-affiliated and non-ESC-affiliated countries, respectively (online supplemental table 4).

Among patients with recurrent IE, 79.4% (n=212) were reinfection and 20.6% (n=55) relapse. No differences in anamnestic data were recorded. There was a trend towards a higher rate of valvular intervention in patients with reinfection (71.7% vs 58.2%; p=0.054). Patients with relapses presented at admission higher BNP values than patients with reinfection (table 1).

Blood cultures were less frequently positive in relapses than reinfections, but infecting microorganisms were similar, with *S. aureus* being the most frequently isolated microorganism followed by enterococci and coagulase-negative staphylococci. Considering complications while on therapy, patients with relapse developed more frequently symptomatic stroke compared with patients with reinfection. In-hospital mortality was higher in patients with relapse than in those with reinfection (27.3% vs 15.6%; p=0.044).

Special population group: intravenous drug users

Among patients with recurrent IE, IVDU was reported in 35 (13.2%) patients. IVDUs were younger than non-IVDUs with a lower incidence of comorbidities. At admission, pulmonary embolism was more frequently observed in IVDUs than in non-IVDUs (online supplemental table 5).

Among patients with recurrent IE, *S. aureus* was also the most frequently isolated microorganism in IVDUs, with a high rate of methicillin-resistant *S. aureus*. A higher rate of enterococci was detected in IVDUs with recurrent IE as compared with IVDUs with first-episode IE.

IVDU patients with recurrent IE showed a higher complication rate while on therapy than non-IVDUs, including septic shock, persistent fever, increasing vegetation size and pulmonary embolism.

In-hospital mortality was higher in IVDUs with recurrent IE than in IVDUs with a first episode of IE (25.7% vs 11.3%; p=0.032) but similar to non-IVDUs with recurrent IE.

Survival analysis

Predictors of in-hospital mortality

In the matched cohorts with recurrent IE or first-episode IE, severe valvular regurgitation (p<0.001), isolation of methicillin-sensitive *S. aureus* (p=0.001), signs of congestive heart failure at admission (p=0.007), failure to undertake surgery when indicated (p=0.010), mechanical mitral valve (p=0.004) and occurrence of septic shock while on therapy (p=0.002) were independent predictors of in-hospital mortality (online supplemental table 6).

Multivariable analysis among patients with relapse and reinfection showed that occurrence of complications at admission (severe valvular regurgitation) and under therapy (cardiogenic and septic shock) and failure to undertake surgery when indicated were independent predictors of in-hospital mortality (table 3).

Predictors of 1-year mortality

In the matched cohort, no differences in mortality were recorded at follow-up between patients with recurrent IE and a first episode of IE (figure 2). In both groups, independent predictors of mortality at follow-up were a history of chronic renal failure, occurrence of septic shock, congestive heart failure while on therapy, isolation of methicillin-sensitive *S. aureus* and failure to undertake surgery when indicated (figure 3 and online supplemental figure 1).

Multivariable analysis showed no differences in 1-year mortality between patients with relapse and reinfection (p=0.954). NYHA class III/IV at admission, occurrence of cardiogenic shock at presentation, occurrence of septic shock, embolic events while on therapy and failure to undertake surgery when indicated were found to be independent predictors of 1-year mortality (online supplemental table 7).

Kaplan-Meier survival analysis showed no differences in in-hospital course and outcome at follow-up for patients with a first episode of IE compared with those with recurrent IE (figure 2), even after excluding patients with negative blood culture (online supplemental figures 1-3). Presence of repaired or prosthetic valve was not associated with in-hospital and post-hospitalisation mortality compared with IE in the native valve (online supplemental table 5C,D).

DISCUSSION

The key findings of this largest contemporary series of recurrent IE are as follows: (i) recurrent IE accounted for 8.6% of IE admissions and IVDU was a frequent predisposing factor; (ii) recurrent IE was not a risk factor for in-hospital death and showed similar in-hospital and long-term mortality in comparison with first-episode IE; (iii) occurrence of complications at admission and while on therapy, and failure to undertake surgery when indicated are independent predictors of in-hospital mortality in patients with first-episode and recurrent IE; (iv) among patients

Table 1 Characteristics of the study population

Variable	Total n=3113	First-episode IE n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P value (first-episode IE vs recurrent IE)	Recurrent reinfection n=212 (79.4%)	Recurrent relapse n=55 (20.6%)	P value (reinfection vs relapse)
Male sex	2144/3113 (68.9%)	1938/2839 (68.3%)	200/267 (74.9%)	0.044	162/212 (76.4%)	38/55 (69.1%)	0.264
Age (years)	59.3 (±18.0)	59.4 (±18.1)	58.1 (±17.7)	0.359	57.6 (±17.2)	59.7 (±19.6)	0.285
Medical history							
Congenital heart disease	365/3111 (11.7%)	332/2837 (11.7%)	32/267 (12.0%)	0.969	24/212 (11.3%)	8/55 (14.5)	0.512
Bicuspid aortic valve	200/3103 (6.4%)	185/2829 (6.5%)	14/267 (5.2%)	0.498	11/212 (5.2%)	3/55 (5.5%)	1.000
Pacemaker	325/3113 (10.4%)	291/2839 (10.3%)	33/267 (12.4%)	0.281	28/212 (13.2%)	5/55 (9.1%)	0.408
Valvular intervention	1023/3113 (32.9%)	833/2839 (29.3%)	184/267 (68.9%)	<0.001	152/212 (71.7%)	32/55 (58.2%)	0.054
Intravascular catheter	168/2844 (5.9%)	147/2603 (5.6%)	20/234 (8.5%)	0.127	16/185 (8.6%)	4/49 (8.2%)	1.000
Risk factors/Clinical conditions							
History of congestive heart failure	661/2837 (23.3%)	581/2597 (22.4%)	80/233 (34.3%)	<0.001	61/185 (33.0%)	19/48 (39.6%)	0.390
Arterial hypertension	1499/3108 (48.2%)	1370/2835 (48.3%)	125/266 (47.0%)	0.798	98/211 (46.4%)	27/55 (49.1%)	0.726
Chronic renal failure	551/3110 (17.7%)	495/2836 (17.5%)	53/267 (19.9%)	0.135	39/212 (18.4%)	14/55 (25.5%)	0.242
Dialysis	163/3110 (5.2%)	146/2836 (5.1%)	15/267 (5.6%)	0.02	11/212 (5.2%)	4/55 (7.3%)	0.520
Diabetes mellitus	704/3109 (22.6%)	652/2836 (23.0%)	51/266 (19.2%)	0.316	40/211 (19.0%)	11/55 (20.0%)	0.861
Intravenous drug users	212/3064 (6.9%)	177/2792 (6.3%)	35/265 (13.2%)	<0.001	30/210 (14.3%)	5/55 (9.1%)	0.311
Intravenous catheter	250/3101 (8.1%)	227/2827 (8.0%)	20/267 (7.5%)	0.003	13/212 (6.1%)	7/55 (12.7%)	0.145
Charlson Comorbidity Index	N=2631	N=2398	N=229		N=182	N=47	
	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–5.0)	0.211	3.4 (±2.6)	4.1 (±3.6)	
Clinical findings at admission							
Time since symptom onset (days)	N=3000	N=2737	N=256	<0.001	N=205	N=51	0.344
	14.0 (4.0–40.0)	15.0 (4.0–41.0)	8.5 (2.0–30.5)		9.0 (2.0–31.0)	7.0 (1.0–22.0)	
Data from symptom onset to hospitalisation >30 days	966/3000 (32.2%)	901/2737 (32.9%)	64/256 (25.0%)	0.016	138/197 (70.1%)	9/51 (17.6%)	0.175
Prosthetic/Repair valve	939/3008 (31.2%)	769/2754 (27.9%)	164/247 (66.4%)		46/197 (23.4%)	26/50 (52.0%)	
Native valve	1763/3008 (58.6%)	1696 (61.6%)	66/247 (26.7%)	<0.001	13/197 (6.6%)	20/50 (40.0%)	0.045
ICD/PM	306/3008 (10.2%)	289/2754 (10.5%)	17/247 (6.9%)		17/247 (6.9%)	4/50 (8.0%)	
NYHA class I	1101/2915 (37.8%)	1008/2667 (37.8%)	92/241 (38.2%)		74/189 (39.2%)	18/52 (34.6%)	
II	1002/2915 (34.4%)	904/2667 (33.9%)	92/241 (38.2%)	0.106	69/189 (36.5%)	23/52 (44.2%)	0.423
III	592/2915 (20.3%)	547/2667 (20.5%)	45/241 (18.7%)		38/189 (20.1%)	7/52 (13.5%)	
IV	220/2915 (7.5%)	208/2667 (7.8%)	12/241 (5.0%)		8/189 (4.2%)	4/52 (7.7%)	
Congestive heart failure	846/3113 (27.2%)	786/2839 (27.7%)	59/267 (22.1%)	0.109	45/212 (21.2%)	14/55 (25.5%)	0.501
BNP (pmol/L)	N=381	N=346	N=35		N=24	N=11	
	1186.9	1190.3	1173.0	0.975	777.2	2311.4	0.008
	(366.8-2941.2)	(366.8-2941.2)	(529.1-3017.3)		(187.9-1508.7)	(1055.4-5173.0)	
NT-proBNP (pmol/L)	N=542	N=493	N=47		N=34	N=13	
	22 521	24 695	11 864	0.021	12 894	4237	0.335
	(5525–84 746)	(6220–85 788)	(3390–30 941)		(4460–26 475)	(2907–41 975)	
Cardiogenic shock	63/2837 (2.2%)	61/2597 (2.3%)	2/233 (0.9%)	0.309	2/185 (1.1%)	0/48 (0.0%)	1.000
Septic shock	203/3112 (6.5%)	183/2838 (6.4%)	20/267 (7.5%)	0.63	14/212 (6.6%)	6/55 (10.9%)	0.263
Embolic events	791/3113 (25.4%)	732/2839 (25.8%)	59/267 (22.1%)	0.126	44/212 (20.8%)	15/55 (27.3%)	0.299
Cerebral	350/3113 (11.2%)	327/2839 (11.5%)	23/267 (8.6%)	0.229	18/212 (8.5%)	5/55 (9.1%)	0.794
Pulmonary	195/3113 (6.3%)	175/2839 (6.2%)	20/267 (7.5%)	0.549	12/212 (5.7%)	8/55 (14.5%)	0.040
Splenic	176/3113 (5.7%)	166/2839 (5.8%)	10/267 (3.7%)	0.295	8/212 (3.8%)	2/55 (3.6%)	1.000
Renal	76/3113 (2.4%)	74/2839 (2.6%)	2/267 (0.7%)	0.156	2/212 (0.9%)	0/55 (0%)	1.000
Peripheral	92/3113 (3.0%)	80/2839 (2.8%)	12/267 (4.5%)	0.272	9/212 (4.2%)	3/55 (5.5%)	0.716
Other	76/3113 (2.4%)	74/2839 (2.6%)	2/267 (0.7%)	0.156	2/212 (0.9%)	0/55 (0%)	1.000
Haemorrhagic stroke	67/3113 (2.2%)	62/2839 (2.2%)	5/267 (1.9%)	0.875	3/212 (1.4%)	2/55 (3.6%)	0.274
Spondylitis	168/3113 (5.4%)	156/2839 (5.5%)	11/267 (4.1%)	0.37	8/212 (3.8%)	3/55 (5.5%)	0.702
Microbiological findings							
Positive blood culture	2458/3113 (79.0%)	2232/2839 (78.6%)	221/267 (82.8%)	0.25	184/212 (86.8%)	37/55 (67.3%)	<0.001
Staphylococcus aureus	765/3113 (24.6%)	693/2839 (24.4%)	72/267 (27.0%)	0.207	60/212 (28.3%)	12/55 (21.8%)	0.334
Methi-S *S. aureus*	593/3113 (19.0%)	533/2839 (18.8%)	60/267 (22.5%)	0.148	50/212 (23.6%)	10/55 (18.2%)	0.392
Methi-R *S. aureus*	177/3113 (5.7%)	165/2839 (5.8%)	12/267 (4.5%)	0.545	10/212 (4.7%)	2/55 (3.6%)	1.000
CoNS	307/3113 (9.9%)	286/2839 (10.1%)	21/267 (7.6%)	0.248	18/212 (8.5%)	3/55 (5.4%)	0.456
Methi-S CoNS	163/3113 (5.2%)	152/2839 (5.4%)	11/267 (4.1%)	0.566	10/212 (4.7%)	1/55 (1.8%)	0.469
Methi-R CoNS	150/3113 (4.8%)	140/2839 (4.9%)	10/267 (3.7%)	0.576	8/212 (3.8%)	2/55 (3.6%)	1.000
Viridans group streptococci	304/3113 (9.8%)	283/2839 (10.0%)	21/267 (7.9%)	0.371	19/212 (9.0%)	2/55 (3.6%)	0.265
Enterococcus	389/3113 (12.5%)	338/2839 (11.9%)	49/267 (18.4%)	0.004	39/212 (18.4%)	10/55 (18.2%)	0.971

Continued

Table 1 Continued

Variable	Total n=3113	First-episode IE n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P value (first-episode IE vs recurrent IE)	Recurrent reinfection n=212 (79.4%)	Recurrent relapse n=55 (20.6%)	P value (reinfection vs relapse)
Streptococcus bovis	162/3113 (5.2%)	151/2839 (5.3%)	11/267 (4.1%)	0.578	11/212 (5.2%)	0/55 (0.0%)	0.127
Gram-negative bacillus	86/3113 (2.8%)	82/2839 (2.9%)	4/267 (1.5%)	0.376	2/212 (0.9%)	2/55 (3.6%)	0.189
Other positive culture	579/3113 (18.6%)	527/2839 (18.6%)	50/267 (18.7%)	0.793	40/212 (18.9%)	10/55 (18.2%)	0.907
Echocardiographic findings							
Aortic valve	1403/3108 (45.1%)	1293/2835 (45.6%)	105/266 (39.5%)	0.061	88/212 (41.5%)	17/54 (31.5%)	0.178
Mitral valve	1313/3108 (42.2%)	1201/2835 (42.4%)	109/266 (41.0%)	0.911	88/212 (41.5%)	21/54 (38.9%)	0.727
Tricuspid valve	453/3108 (14.6%)	399/2835 (14.1%)	54/266 (20.3%)	0.012	42/212 (19.8%)	12/54 (22.2%)	0.694
ICD/PM/Other	269/3108 (8.7%)	251/2835 (8.9%)	18/266 (6.8%)	0.367	14/212 (6.6%)	4/54 (7.4%)	0.767
Vegetation	2258/3108 (72.7%)	2089/2835 (73.7%)	167/266 (62.8%)	<0.001	136/212 (64.2%)	31/54 (57.4%)	0.360
Vegetation maximal length	N=1894	N=1755	N=137		N=110	N=27	
	12.0 (8.0–18.0)	12.0 (8.0–18.0)	11.0 (7.0–17.0)	0.034	11.0 (7.0–16.0)	12.0 (8.0–18.0)	0.549
Abscess	323/3108 (10.4%)	286/2835 (10.1%)	36/266 (13.5%)	0.2	31/212 (14.6%)	5/54 (9.3%)	0.304
Pseudoaneurysm	108/3108 (3.5%)	95/2835 (3.4%)	13/266 (4.9%)	0.375	12/212 (5.7%)	1/54 (1.9%)	0.477
Fistula	52/3108 (1.7%)	45/2835 (1.6%)	7/266 (2.6%)	0.294	5/212 (2.4%)	2/54 (3.7%)	0.633
Paraprosthetic regurgitation	202/3108 (6.5%)	159/2835 (5.6%)	39/266 (14.7%)	<0.001	31/212 (14.6%)	8/54 (14.8%)	0.972
New prosthetic dehiscence	105/3108 (3.4%)	80/2835 (2.8%)	25/266 (9.4%)	<0.001	22/212 (10.4%)	3/54 (5.6%)	0.278
Severe regurgitation	1179/3108 (37.9%)	1100/2835 (38.8%)	79/266 (29.7%)	0.001	62/212 (29.2%)	17/54 (31.5%)	0.748
Severe stenosis	195/3108 (6.3%)	176/2835 (6.2%)	18/266 (6.8%)	0.639	14/212 (6.6%)	4/54 (7.4%)	0.767
Perforation	275/3108 (8.8%)	256/2835 (9.0%)	19/266 (7.1%)	0.416	13/212 (6.1%)	6/54 (11.1%)	0.235
Right ventricular dysfunction	401/2832 (14.2%)	353/2593 (13.6%)	48/232 (20.7%)	0.007	37/185 (20.0%)	11/47 (23.4%)	0.607
Right ventricular systolic pressure	N=1772	N=1593	N=175		N=137	N=38	
	38 (30–50)	38 (30–50)	35 (28–48)	0.397	35 (28–45)	37 (26–60)	0.193
LVEF (%)	N=2657	N=2428	N=222		N=173	N=49	
	58 (50–64)	58 (50–65)	55 (50–62)	0.24	56 (50–65)	55 (50–60)	0.021

Values are expressed as mean (SD) or n (%).
BNP, B-type natriuretic peptide; CoNS, coagulase-negative staphylococci; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; LVEF, left ventricular ejection fraction; Methi-R, methicillin-resistant; Methi-S, methicillin-sensitive; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker.

with recurrent IE, IVDUs and patients with IE relapse showed higher in-hospital mortality than non-IVDUs and patients with reinfection.

Recurrent versus first-episode infective endocarditis

In the largest cohort of patients to date with recurrent IE enrolled in the EURO-ENDO registry, the incidence of recurrent IE was about 8.9% and 8.2% in ESC-affiliated and non-ESC-affiliated countries, respectively. Although previous studies included smaller study populations, recurrence rates gradually decreased over the last decades, from 33% in the study by Welton *et al* to over 8.1% in the study by Freitas-Ferraz *et al*.[7 10]

Several studies demonstrated a higher incidence of previous valvular intervention and complications related to periprosthetic and prosthetic damage in patients with recurrent IE compared with those with first-episode IE.[10 11] *S. aureus* has been the most frequently isolated microorganism in patients with recurrent IE, often in IVDUs and related to prosthetic IE.[4 12] In our population, an increased rate of enterococci was found in patients with recurrent IE versus patients with first-episode IE. This is consistent with the results of Pericàs *et al* showing increased recurrence rates in a large cohort of enterococcal endocarditis, correlated with a higher rate of persistent bacteraemia.[12–14]

Our study confirmed the higher incidence of previous valvular intervention in patients with recurrent IE and also demonstrated a lower severity of valvular and paravalvular regurgitation in recurrent IE compared with first-episode IE. These findings could be due to some peculiar differences between groups. Patients with recurrent IE had a shorter delay between symptom onset and hospitalisation (IQR 4.0–41.0) than in patients with a first episode of IE. This could have resulted in longer exposure time to a persistent infectious and inflammatory process without appropriate antibiotic therapy in patients with first-episode IE, leading to greater valvular damage and more complications at admissions and during hospitalisation. Of note, patients with first-episode IE presented more often with signs of congestive heart failure, also confirmed by higher NT-proBNP level. In contrast, in patients with recurrent IE, a lower complication rate at admission and during hospitalisation could be due to an increased awareness of IE symptoms at the time of the recurrent event.[10 15]

Reinfection versus relapse

The incidence of a second episode of IE ranges from 2% to 22%,[9] involving especially IVDUs and patients with a prosthetic valve. Only few studies investigated differences between relapse and reinfection, partly due to difficulties in defining these two events.[16] The large population of EURO-ENDO provided more information about this aspect. In our analysis, relapses were associated with higher BNP level at admission, reduced left ventricular ejection fraction, occurrence of stroke during antibiotic therapy and increased in-hospital mortality compared with reinfections. Of note, patients with relapse had a lower rate of positive blood cultures, probably due to antibiotic therapy employed for the previous IE episode, selecting resistant microorganism and reducing the effect of antibiotic therapy. The infectious burden and the persistent inflammatory pathway resulted in increased mortality in patients at very high surgical risk and an inadequate response to antibiotic therapy.

Among patients with recurrent IE, IVDUs presented more often with cardiac and systemic complications at admission. At admission, cerebral abscess, pulmonary embolism, larger vegetations and paravalvular damage after prosthesis repair or replacement are

Table 2 In-hospital and follow-up events

Variable	Total n=3113	First-episode IE n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P value (first-episode IE vs recurrent IE)	Recurrent reinfection n=212 (79.4%)	Recurrent relapse n=55 (20.6%)	P value (reinfection vs relapse)
Complications under therapy							
Embolic events	641/3113 (20.6%)	582/2839 (20.5%)	59/267 (22.1%)	0.333	46/212 (21.7%)	13/55 (23.6%)	0.758
Cerebral	283/3113 (9.1%)	258/2839 (9.1%)	25/267 (9.4%)	0.696	17/212 (8.0%)	8/55 (14.5%)	0.139
Pulmonary	171/3113 (5.5%)	153/2839 (2.8%)	18/267 (6.7%)	0.531	15/212 (7.1%)	3/55 (5.5%)	1.000
Splenic	139/3113 (4.5%)	127/2839 (4.5%)	12/267 (4.5%)	0.849	9/212 (4.2%)	3/55 (5.5%)	0.716
Renal	58/3113 (1.9%)	51/2839 (1.8%)	7/267 (2.6%)	0.428	6/212 (2.8%)	1/55 (1.8%)	1.000
Peripheral	60/3113 (1.9%)	55/2839 (1.9%)	5/267 (1.9%)	0.931	3/212 (1.4%)	2/55 (3.6%)	0.274
Other	52/3113 (1.7%)	48/2839 (1.7%)	4/267 (1.5%)	1.000	4/212 (1.9%)	0/55 (0.0%)	0.584
Haemorrhagic stroke	79/3113 (2.5%)	74/2839 (2.6%)	5/267 (1.9%)	0.700	3/212 (1.4%)	2/55 (3.6%)	0.274
Spondylitis	145/3113 (4.7%)	137/2839 (4.8%)	8/267 (3.0%)	0.366	7/212 (3.3%)	1/55 (1.8%)	1.000
Stroke	168/3113 (5.4%)	153/2839 (5.4%)	15/267 (5.6%)	0.808	8/212 (3.8%)	7/55 (12.7%)	0.018
Congestive heart failure	436/3113 (14.0%)	395/2839 (13.9%)	40/267 (15.0%)	0.891	30/212 (14.2%)	10/55 (18.2%)	0.455
Cardiogenic shock	189/2837 (6.7%)	171/2597 (6.6%)	18/233 (7.7%)	0.622	13/185 (7.0%)	5/48 (10.4%)	0.542
Septic shock	287/3113 (9.2%)	259/2839 (9.1%)	28/267 (10.5%)	0.534	20/212 (9.4%)	8/55 (14.5%)	0.270
Acute renal failure	548/3113 (17.6%)	508/2839 (17.9%)	39/267 (14.6%)	0.392	30/212 (14.2%)	9/55 (16.4%)	0.679
Persistent fever	350/2837 (12.3%)	321/2597 (12.4%)	29/233 (12.4%)	0.610	24/185 (13.0%)	5/48 (10.4%)	0.633
Increasing vegetation size	201/3113 (6.5%)	178/2839 (6.3%)	23/267 (8.6%)	0.259	18/212 (8.5%)	5/55 (9.1%)	0.794
EuroSCORE II	N=2632 5.0 (2.0–13.3)	N=2399 4.8 (1.9–12.9)	N=230 7.4 (3.7–17.5)	<0.001	N=181 7.4 (3.8–16.0)	N=49 6.8 (3.2–19.9)	0.974
Duration of antibiotic therapy (days)	64.0 (40.0; 97.0)	63.0 (40.0; 96.0)	69.5 (43.0; 105.0)	0.196	70.5 (42.0; 106.0)	64.0 (43.0; 91.0)	0.584
Theoretical indication to surgery	2157/3112 (69.3%)	1971/2838 (69.5%)	182/267 (68.2%)	0.631	143/212 (67.5%)	39/55 (70.9%)	0.624
Performed surgery	1596/2157 (74.0%)	1475/1971 (74.8%)	118/182 (64.8%)	0.012	97/143 (67.8%)	21/39 (53.8%)	0.105
Haemodynamic indication	996/3112 (32.0%)	918/2838 (32.3%)	77/267 (28.8%)	0.355	58/212 (27.4%)	19/55 (34.5%)	0.294
Embolic indication	693/3112 (22.3%)	639/2838 (22.5%)	54/267 (20.2%)	0.253	47/212 (22.2%)	7/55 (12.7%)	0.120
Infectious indication	1384/3112 (44.5%)	1253/2838 (44.2%)	128/267 (47.9%)	0.472	99/212 (46.7%)	29/55 (52.7%)	0.425
In-hospital death	529/3113 (17.0%)	481/2839 (16.9%)	48/267 (18.0%)	0.445	33/212 (15.6%)	15/55 (27.3%)	0.044
Events at follow-up							
1-year mortality	235/2126 (11.1%)	210/1938 (10.8%)	24/184 (13.0%)	0.271	17/149 (11.4%)	7/35 (20.0%)	0.174
Recurrence	67/1605 (4.2%)	53/1469 (3.6%)	14/133 (10.5%)	0.002	10/108 (9.3%)	4/25 (16.0%)	0.299
Congestive heart failure	316/1639 (19.3%)	276/1494 (18.5%)	40/143 (28.0%)	0.020	32/117 (27.4%)	8/26 (30.8%)	0.725

Values are expressed as mean (SD) or n (%).
IE, infective endocarditis.

often detected in recurrent IVDUs compared with IVDUs at first IE episode and recurrent IE non-IVDUs. In addition, the clinical management of recurrent IE in IVDUs could be influenced by treatment of the previous episode: occurrence of antibiotic resistance in patients infected with the same microorganism (staphylococci), increased surgical risk and less cardiac reintervention, resulted in higher in-hospital mortality compared with first-episode IE IVDUs[17 18] and recurrent IE non-IVDUs.

Survival analysis

Our study is the first to use propensity matching to adjust for relevant clinical characteristics and showed that recurrent IE did not negatively impact in-hospital and 1-year mortality consistent with the results of Freitas-Ferraz *et al*.[10]

Complications occurring at admission or during therapy, including cardiogenic or septic shock and absence of surgery when indicated, were independently associated with in-hospital and 1-year mortality both in patients with a first episode of IE and those with recurrent IE (either relapse or reinfection), in line with the results of the EURO-ENDO study.[3] This finding highlights how the infective-inflammatory burden related to infectious disease may affect the prognosis, regardless of epidemiological and clinical differences between groups (first-episode IE vs recurrent IE and relapse vs reinfection). Chu *et al* investigated

Table 3 Multivariate Cox proportional hazard models performed in patients with relapse and reinfection as a predictor of in-hospital mortality (cut-off used at 30 days and with inclusion date as reference)

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P value global	Modality	HR (95% CI)	P value
232/267	Stat=16.27 with 9 df and 10 groups P=0.061	0.8366	IE relapse versus reinfection	0.919	IE relapse versus reinfection	0.95 (0.34 to 2.68)	0.919
			Severe valvular regurgitation	0.013	Yes versus no	3.14 (1.27 to 7.76)	0.013
			Cardiac surgery	0.027	Indication—not performed	6.26 (1.61 to 24.38)	0.008
					No indication	3.58 (0.81 to 15.75)	0.092
			Complications under therapy—septic shock	<0.001	Yes versus no	6.70 (2.73 to 16.43)	<0.001
			Clinical examination—cardiogenic shock	0.009	Yes versus no	18.34 (2.10 to 160.53)	0.009

df, degree of freedom; IE, infective endocarditis.

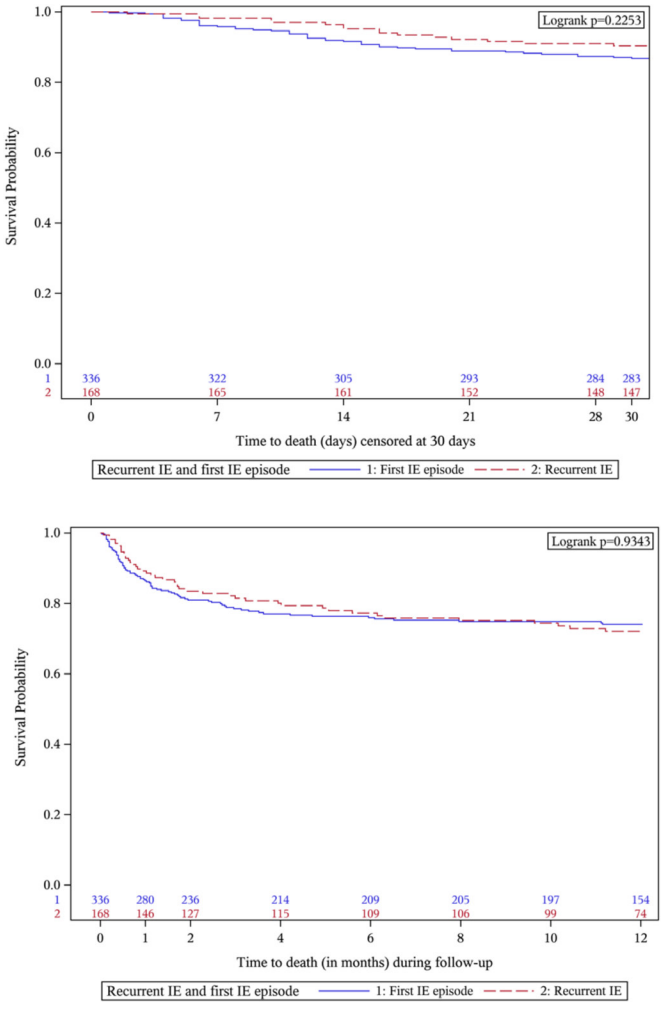

Figure 2 Kaplan-Meier survival curves during hospitalisation (upper panel) and at 1-year follow-up (lower panel) in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE).

the early in-hospital prognostic role of the Acute Physiology And Chronic Health Evaluation (APACHE) II score in IE, taking into account many clinical parameters reflecting inflammatory burden and organ damage related to infection[19] to better identify clinical profile of patients at risk of poor outcome. Cardiac surgery was inversely associated with in-hospital and 1-year

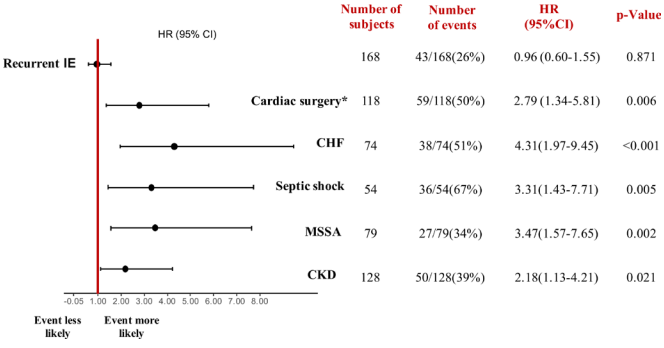

Figure 3 Forest plot of multivariable Cox proportional hazards models in matched cohort for recurrent and non-recurrentinfective endocarditis (IE) as a predictor of mortality at follow-up. *Cardiac surgery indicated but not performed. CHF, congestive heart failure; CKD, chronic kidney disease; MSSA, methicillin-susceptible *Staphylococcus aureus.*

mortality similar to what we observed in the present study and what has been reported in the overall population of the EURO-ENDO study.[3]

Study limitations

This study is an ancillary analysis of EURO-ENDO and it carries with it the limitations of a multicentre, observational study. However, the high number of enrolled patients and the several centres involved, provided a realistic picture of epidemiological aspects and management of patients with IE. In this ancillary analysis, patients with first-episode and recurrent IE were evaluated for in-hospital and 1-year follow-up outcomes. A propensity-based matching approach was used for survival analysis creating patient samples with recurrent and non-recurrent IE with similar characteristics to assess predictors of in-hospital and follow-up mortality.

An additional limitation regarding the comparison between IE relapse and reinfection is that data on the previous episode of IE are missing, particularly in-hospital course, therapy and type of surgery performed. Nevertheless, to the best of our knowledge, this study provides the largest and most detailed prospectively collected data on patients with IE including the largest sample size of relapses and reinfections ever described in the literature. The definitions of IE recurrent relapse and reinfection were arbitrarily chosen following the data published at the time of enrolment.

CONCLUSIONS

Patients with recurrent IE had similar in-hospital and 1-year mortality compared with patients with first-episode IE, and both groups shared similar predictors of poor outcome. Independent predictors of poorer in-hospital and 1-year outcome were the occurrence of cardiogenic and septic shock, valvular disease severity and failure to undertake surgery when indicated. Recurrence of IE was often observed in patients with valvular prosthesis and was associated with paravalvular complications and staphylococci infection. In patients with recurrent IE, IVDUs patients and patients with IE relapse had poorer outcome due to higher in-hospital complication rates compared with non-IVDUs and patients with reinfection.

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