Clinical profile and outcome of recurrent infective endocarditis

Rodolfo Citro, Kwan-Leung Chan, Marcelo Haertel Miglioranza, Cécile Laroche, Rossella Maria Benvenga, Shumaila Furnaz, Julien Magne, Carmen Olmos, Bernard Paelinck, Agnès Pasquet, et al.

Clinical profile and outcome of recurrent infective endocarditis Insights from the ESC EORP EURO-ENDO registry.

Authors list

Rodolfo Citro[1], Chan Kwan-Leung[2], Marcelo Haertel Miglioranza[3], Cécile Laroche[4], Rossella Maria Benvenga[1], Shumaila Furnaz[5], Abdelrahman AM Jamiel[6], Julien Magne[7,8], Carmen Olmos[9], Bernard P. Paelinck[10], Agnès Pasquet[11], Cornelia Piper[12], Antonio Salsano[13], Arnaud Savouré[14], Seung Woo Park[15], Piotr Szymański[16], Pierre Tattevin[17], Nuria Vallejo Camazon[18], Patrizio Lancellotti[19,20], Gilbert Habib[21].

On behalf of the EURO ENDO Investigators group*

*Listed in Appendix 1.

Affiliations

[1] University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy

[2] University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, Ontario, Canada K1Y 4W7

[3] Institute of Cardiology–University Foundation of Cardiology, Porto Alegre, Brazil; and the Mae de Deus Hospital, Porto Alegre, Brazil

[4] EORP, European Society of Cardiology, Sophia-Antipolis, France

[5] Department of Research, National Institute of Cardiovascular diseases Karachi, Pakistan

[6] Consultant Cardiologist at King Abdulaziz Medical City for national Guard
Assistant professor adult cardiology at King Saud bin Abdulaziz University for health specialities, Riyadh, Saudi Arabia

[7] CHU Limoges, Hôpital Dupuytren, Service Cardiologie, Limoges, F-87042, France.

[8] INSERM 1094, Faculté de médecine de Limoges, 2, rue Marcland, 87000 Limoges, France.

[9] Instituto Cardiovascular, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdSSC), Madrid, Spain

[10] Antwerp University Hospital dept. Cardiac Surgery, Wilrijkstraat 10, Edegem 2650, Belgium

[11] Division of Cardiology, Department of Cardiovascular Diseases, Cliniques Universitaires St. Luc Pôle de Recherche Cardiovasculaire (CARD) Institut de Recherche Expérimentale et Clinique (IREC) Université Catholique de Louvain, Brussels, Belgium

[12] Clinic for General and Interventional Cardiology/Angiology, Herz- und Diabeteszentrum NRW, Ruhr-Universität Bochum, Bad Oeynhausen, Germany

[13] Division of Cardiac Surgery, Ospedale Policlinico San Martino, University of Genoa, DISC Department, Genoa, Italy

[14] Cardiology Department, University Hospital of Rouen, France

[15] Professor of Medicine, Heart Stroke Vascular Institute, Sungkyunkwan University School of Medicine, Samsung Medical Center

[16] Noninvasive Cardiovascular Diagnostic Department, Central Clinical Hospital of MSWiA, Warsaw, Poland and Center for Postgraduate Medical Education, Warsaw, Poland

[17] Pierre Tattevin, Infectious diseases and Intensive care unit, Pontchaillou University Hospital, Rennes, France

[18] Heart Institute, Hospital Universitari Germans Trias i Pujol, Badalona, Barcelona, Spain

[19] University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology and Cardiovascular Surgery, CHU Sart Tilman, Liège, Belgium

[20] Gruppo Villa Maria Care and Research, Maria Cecilia Hospital, Cotignola, and Anthea Hospital, Bari, Italy

[21] Service de Cardiologie, Hôpital La Timone, Boulevard Jean Moulin, Marseille France

Corresponding Author

ORCID ID https://orcid.org/0000-0002-7796-6298

Rodolfo Citro MD, PhD, FESC

Cardio-Thoracic-Vascular Department

University Hospital “San Giovanni di Dio e Ruggi d’Aragona”

Heart Tower, room 807

Largo Città di Ippocrate, Salerno 84131, Italy.

Phone: 0039089673377 - Mobile 00393473570880 - Fax: 0039089673314

E-mail: rodolfocitro@gmail.com

ABSTRACT = 250 words max

Aims: Recurrent infective endocarditis (IE) is recognized to be associated with increased risk of complications and poor outcome.

Methods: Recurrent IE was defined as an episode of IE occurring ≤6 months after a previous episode caused by the same microorganism (relapse); or >6 months, caused by the same or another microorganism (reinfection). Patients (pts) never hospitalized for IE were considered at first episode of EI. Aim of this study was to evaluate predictors of in-hospital and 1-year mortality both in recurrent and first-IE episode pts, enrolled in the largest to date, multicenter European Society of Cardiology (ESC) EURObservational Research Programme (EORP) European Infective Endocarditis (EURO-ENDO) registry from January 2016 to March 2018.

Results: Recurrences were 267 (8.6%), 13.2% were intravenous drug abusers (IVDAs), 68.9% had a history of valvular surgery. Staphylococci were the most frequently isolated microorganism. Recurrent relapse and reinfection were 20.6% and 79.4%, respectively. Pts at first episode of IE were 2839 (91.4%), showed at admission congestive heart failure (27.7%) and severe valvular regurgitation (38.8%). At multivariable Cox proportional hazard models performed in a matched cohort for both groups, recurrent IE was inversely associated with in-hospital mortality compared to first-episode IE (hazard ratio 0.17, 95% confidence interval 0.04-0.71; P=0.015). At 1-year follow-up, there were no differences in mortality between recurrent and first-episode IE pts. Among recurrences, in-hospital mortality was increased in pts with relapse and IVDAs.

Conclusion: Pts with recurrent IE seem to show lower rates of IE-related complications, both at admission and during hospitalization, compared with pts at first episode of IE.

Keywords: max 6

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 the largest multicenter registry to date, which enrolled 3116 patients with IE from European Society of Cardiology (ESC) and non-ESC affiliated countries and analyzed the epidemiological and microbiological findings and clinical course during hospitalization and at 1-year follow-up[2]. The recently published results of EURO-ENDO demonstrate that patients affected by IE are older and have multiple comorbidities, and absence of surgery when indicated is associated with a worse outcome[3]. A number of studies assessed the predictors of poor prognosis to identify patients at high risk and improve their management during hospitalization. Although several studies reported that recurrent IE is associated with a poor prognosis, a knowledge gap still exists about microbiological and clinical findings that may correlate with a worse outcome[4-7].

The objectives of this study were to examine the clinical features of patients with recurrent IE and to evaluate the clinical course and outcome by comparison with a propensity-matched group of first-episode IE patients.

METHODS

The EURO-ENDO registry is a multicenter, prospective observational study that enrolled all consecutive patients aged <18 years with a diagnosis of definite or possible IE according to the ESC guidelines[8], who referred to hospitals of ESC-affiliated/non-affiliated countries from 1 January 2016 to 31 March 2018[2].

Patients who had never been hospitalized for IE were defined as experiencing first-episode IE. Conversely, recurrent IE was defined as an episode of IE occurring ≤6 months after a previous episode caused by the same microorganism or a microorganism of the same species (relapse); or occurring >6 months caused by the same or another microorganism and considered as a new infection (reinfection)[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).

Data about history, demographics, clinical, biological, microbiological, imaging diagnostic findings, medical and surgical treatment, complications under therapy and in-hospital death were collected. Complications and mortality at 1-year follow-up were also analyzed. In order to evaluate the characteristics of IE recurrence, intravenous drug abusers (IVDAs) were also investigated and compared with non-IVDAs and with IVDAs with a first episode of IE.

Data management and statistical analysis

Continuous variables were expressed as mean ± standard deviation, or median and interquartile range (IQR). Comparisons among groups were performed using Kruskal-Wallis test. Categorical variables were expressed as frequency and percentages. Among-group 2 × 2 comparisons were made using Pearson's Chi-squared test or Fisher's exact test if any expected cell count was <5. Plots of the Kaplan-Meier curves for all-cause mortality were performed. Univariable analysis of mortality was performed using a Cox proportional hazard model. 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. 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 on first echo examination at admission, arterial hypertension, chronic obstructive pulmonary disease/asthma, days from symptom onset to hospitalization, embolic events during hospitalization, hemorrhagic stroke, pseudoaneurysm on first echo examination at admission, severe

regurgitation on first echo examination at admission, severe stenosis on first echo examination at admission.

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 standard deviations of the logit of the estimated propensity score. The success of propensity score matching was assessed by checking standardized differences between groups before and after matching, i.e. the absolute difference in sample means divided by an estimate of the pooled standard deviation of the variable, expressed as a percentage (supplemental table 3). Balancing was considered as successful if the standardized differences were less than 10% for variables used for propensity score development. Thirty days 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 version 9.4 (SAS Institute Inc., Cary, NC, USA)

RESULTS

A total of 3113 patients with IE admitted to 156 hospitals in 40 countries were included in the EURO-ENDO registry (3 patients were excluded from the initial population), of whom 267 (8.6%) had recurrent IE and 2839 (91.4%) a first episode of IE. Overall, 214 recurrent IE patients (79.3%) were from ESC-affiliated countries and 53 patients (20.6%) were from outside Europe (non-ESC countries); among these, reinfections and relapses were observed in 212 (79.4%) and 55 (20.6%) patients, respectively (Supplemental Table 1). Demographic, clinical, echocardiographic, and microbiological data of the study population are reported in Table 1.

Recurrent vs first-episode infective endocarditis (Table 1)

Patients with a first episode of IE and those with recurrent IE did not differ in terms of age and Charlson comorbidity index (CCI). In contrast, patients with recurrent IE had more frequent history

of valvular surgery, congestive heart failure or recent colonoscopy and were more often IVDAs. There were no differences between groups in rate of dental procedures or neuro-intervention/surgery. The median days from symptom onset to hospitalization were longer in first episodes of 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) level. At admission, no differences were observed between groups in the occurrence of embolic events, hemorrhagic stroke, and spondylitis. *S. aureus* was the most frequently isolated microorganism in both groups, followed by enterococci and *Streptococcus viridans*. 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. Patients with recurrent IE experienced more frequently right ventricular dysfunction.

There were no differences between groups in complications under therapy (Table 2). In both groups, the major complication despite therapy was embolic event, which occurred in 22.1% and 20.5% of patients with recurrent IE and a first episode of IE, respectively.

Cardiac surgery was less frequently performed in patients with recurrent IE than 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 hemodynamic 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.

Reinfection vs relapse (Table 1)

Among patients with episodes of IE recurrence, 79.4% (n=212) were reinfection and 20.6% (n=55) relapse. No differences in anamnestic data were recorded, except for an increased rate of valvular intervention in patients with reinfection (71.7% vs 58.2%; P= 0.054). Patients with relapses had a similar incidence of heart failure but higher BNP values than patients with reinfection.

Blood cultures were less frequently positive in relapses than reinfections, but isolated microorganisms were similar, with *S. aureus* being the most frequently isolated microorganism followed by enterococci and coagulase-negative staphylococci.

At echocardiography, there were no differences in the valve involved, or in valvular and paravalvular complications between patients with relapses or reinfections. Considering complications under therapy, patients with relapse developed more frequently symptomatic stroke while on therapy compared with patients with reinfection. There were no differences in indications for cardiac surgery and surgery performed between patients with relapses and reinfections. In-hospital mortality was higher in patients with relapse than in those with reinfection (27.3% vs 15.6%; P=0.044).

Special group population: intravenous drug abusers (Supplemental Table 2)

Among patients with recurrent IE, intravenous drug abuse was reported in 35 (13.2%) patients. IVDAs were younger than non-IVDAs with a lower incidence of comorbidities. At admission, pulmonary embolism was more frequently observed in IVDAs than in non-IVDAs.

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

Patients with recurrent IE and IVDAs showed a higher complications rate while on therapy than non-IVDAs, including septic shock, persistent fever, increasing vegetation size, and pulmonary embolism. In-hospital mortality was higher in IVDAs with recurrent IE than in IVDAs with a first episode of IE (25.7% vs 11.3%; P = 0.032) but similar to non-IVDAs with recurrent IE.

Survival analysis

Predictors of in-hospital mortality

At multivariable Cox proportional hazard analysis performed in the matched cohort of patients with a first episode of IE or with recurrent IE, recurrence was inversely associated with in-hospital mortality [hazard ratio (HR) 0.17, 95% confidence interval (CI) 0.04-0.71; P=0.015] (Table 3). The

Kaplan-Meier survival analysis did not reveal differences in-hospital outcome in patients with a first episode of IE compared with those with recurrent IE (Figure 2).

In the matched cohorts with recurrent IE or a first episode of IE, severe valvular regurgitation, isolation of methicillin-sensitive *S. aureus*, signs of congestive heart failure at admission, failure to undertake surgery when indicated, mechanical mitral valve and occurrence of septic shock while on therapy were independent predictors of in-hospital mortality (Table 3). At multivariable analysis, in patients with recurrent IE, no differences were observed in in-hospital mortality between patients with relapses and reinfections (P=0.919) (Table 4). Severe valvular regurgitation, occurrence of cardiogenic and septic shock despite therapy, failure to undertake surgery when indicated were independent predictors of in-hospital mortality in both relapse and reinfection groups.

Predictors of 1-year mortality

At 1-year follow-up, IE recurrence and congestive heart failure were more frequently observed in patients with recurrent IE than in those with a first episode of IE (Table 2).

In the matched cohort, no differences in mortality were recorded at follow-up between patients with recurrent IE and those with a first episode of IE (Figure 3). In both groups, independent predictors of mortality at follow-up were: a history of chronic renal failure, occurrence of septic shock, and congestive heart failure despite therapy, isolation of methicillin-sensitive *S. aureus* and failure to undertake surgery when indicated (Table 5).

At multivariable analysis, there were 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, and embolic events despite therapy, and failure to undertake surgery when indicated were found to be independent predictors of 1-year mortality in both patients with relapse and reinfection (Table 6).

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 intravenous drug abuse was a frequent predisposing factor; (ii) recurrent IE was not a risk factor for in-hospital death and was also associated with lower in-hospital but similar long-term mortality; (iii) in recurrent IE, the risk factors for in-hospital death are severe valvular dysfunction, severe hemodynamic instability, methicillin-resistant *S. aureus* and failure to undertake surgery when indicated; (iv) recurrent IE in IVDAs is associated with higher in-hospital mortality than recurrent IE in non-IVDAs and AVDAs with a first episode of IE; and (v) in recurrent IE, relapse vs reinfection did not impact on in-hospital mortality after adjusting for confounding variables.

Recurrent vs 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 of Welton et al. in 1979 to over 8.1% in that of Freitas-Ferraz et al. in 2019[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 a first episode of IE[10,11]. In line with these findings, *S. aureus* has been the most frequently isolated microorganism in patients with recurrent IE, often in IVDAs and related to prosthetic IE[4,12]. As a novelty, in our population there is an increasing isolation of enterococci in the group with recurrent IE compared with patients with a first episode of IE. This is consistent with the results of Pericàs et al. showing increased recurrence rates in a large cohort of enterococcal endocarditis, correlated to a higher rate of persistent bacteremia[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, first of all a delay between symptom onset and hospitalization (IQR 4.0-41.0) 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, leading to greater valvular damage. Of note, patients with a first episode of IE presented more often with signs of congestive heart failure, also confirmed by higher NT-proBNP level. In this patient subset, our analysis also reported more complications despite therapy than in patients with recurrent IE, such as spondylitis and acute renal failure during antibiotic therapy, though not statistically significant.

In contrast, in patients with recurrent IE, a lower incidence of complications at admission and during hospitalization could be due to a selection bias for which patients surviving to a previous IE episode are at "low risk" of developing complications at the time of a second event, according to the theory of survivor bias[10,15].

Reinfection vs relapse

The incidence of a second episode of IE ranges from 2% to 22%[9], involving especially IVDAs and patients with a prosthetic valve. Only few studies investigated differences between relapse and reinfection, due to difficulties in defining these two events[16]. The large population of EURO-ENDO could provide 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 high surgical risk and an inadequate response to antibiotic therapy.

Among patients with recurrent IE, IVDAs presented more often cardiac and systemic complications at admission, likely due to a delay between symptom onset and hospitalization. At admission, cerebral abscess, pulmonary embolism, larger vegetations and paravalvular damage after

prosthesis repair or replacement are often detected in IVDAs with recurrent IE compared with IVDAs with a first episode of IE. In addition, the clinical management of recurrent IE in IVDAs could be affected by treatment of the previous episode, because of antibiotic resistance in patients infected with the same microorganism (staphylococci) and increased surgical risk, resulting in higher in-hospital mortality compared with IVDAs with a first episode of IE[17,18].

Survival analysis

Our study is the first to use propensity matching to adjust for relevant clinical characteristics, confirming that recurrent IE does not negatively impact in-hospital mortality. Our findings show that first-episode IE should be considered a risk factor for in-hospital death, as previously suggested by Freitas et al[10].

Complications occurring at admissions 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). 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 of IE vs recurrent IE and relapse vs reinfection). Chu et al. investigated the early in-hospital prognostic role of the APACHE II score in IE, taking into account many clinical parameters, reflecting inflammatory burden and organ damage related to infection[19]. Cardiac surgery was inversely associated with in-hospital and 1-year mortality, as also reported in 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 multicenter, observational study. However, the high number of enrolled patients and the several centers involved, provide 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 assessing in-hospital and 1-year follow-up outcome. In order to overcome the deep differences

among groups, a propensity-based matching approach was used for survival analysis, to find predictors of in-hospital and follow-up mortality, creating patient samples with recurrent and non-recurrent IE with similar characteristics. An additional limitation regards comparison among recurrent and reinfection IE, due to the lack of information about management of previous IE episode. Nevertheless, to the best of our knowledge, this study enrolled the highest and most detailed sample size of IE relapses and reinfections never described in the literature.

CONCLUSIONS

The rates of recurrent IE have decreased over the last decades and the occurrence of IE is still associated with valvular prosthetic, paravalvular complications and isolation of staphylococci. In patients with recurrent IE, IVDAs and patients with relapse had a poorer outcome due to higher in-hospital complication rates compared with non-IVDAs and patients with reinfection. Patients with a first episode of IE developed more often valvular damage and signs of heart failure at admissions compared with patients with recurrent IE. 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.

ACKNOWLEDGEMENTS

EORP Oversight Committee, Registry Executive and Steering Committees. The Data collection was conducted by the EORP department of the ESC: Emanuela Fiorucci, as Project Officer; Viviane Missiamenou, Florian Larras, and Rachid Mir Hassaine, as Data Managers. Statistical analyses were performed by Cécile Laroche of the EURObservational Research Programme, European Society of Cardiology, France. Overall activities were coordinated and supervised by Doctor Aldo P. Maggioni (EORP Scientific Coordinator). Special thanks to the EACVI (European Association of CardioVascular Imaging), to the ESC Working Group on Valvular Heart Disease and to the AEPEI (Association pour l'Etude et la Prévention de l'Endocardite Infectieuse) for their support.

FUNDING

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011-2021), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2021), Bayer AG (2009-2018), Boehringer Ingelheim (2009-2019), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2019), Daiichi Sankyo Europe GmbH (2011-2020), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2016), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2020), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2009-2018), Vifor (2019-2022).

DISCLOSURE

To be completed with forms – See updated form dated Feb 2021 attached
A Conflict of Interest statement to be included under the "Disclosure" header in the submitted manuscript. This paragraph should contain all information in the summary section of the completed ICJME form (this can be copy and pasted directly), plus any information from the 'Comments' section of the form that is not incorporated into the summary. If no conflict exists, please state that 'The Author(s) declare(s) that there is no conflict of interest'.

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FIGURE LEGENDS

Figure 1. Flow-chart study design.

Figure 2. Kaplan-Meier survival curves during hospitalization in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE).

Figure 3. Kaplan-Meier survival curves at 1-year follow-up in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE).

Table 1: Characteristics of the study population

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	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

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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%)	0.020	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 dependency	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 3.0 (1.0-5.0)	N=2398 3.0 (1.0-5.0)	N=229 3.0 (1.0-5.0)	0.211	N=182 3.4 (±2.6)	N=47 4.1 (±3.6)	0.248
Clinical findings at admission							
Time since symptom onset (days)	N=3000 14.0 (4.0-40.0)	N=2737 15.0 (4.0-41.0)	N=256 8.5 (2.0-30.5)	<0.001	N=205 9.0 (2.0 -31.0)	N=51 7.0 (1.0 -22.0)	0.344

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
Data from symptom onset to hospitalization >30 days	966/3000 (32.2%)	901/2737 (32.9%)	64/256 (25.0%)	0.016	55/205 (26.8%)	9/51 (17.6%)	0.175
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
NT-proBNP (pmol/L)	N=542 22 521 (5525-84 746)	N=493 24 695 (6220-85 788)	N=47 11864 (3390-30941)	0.021	N=34 12 894 (4460-26 475)	N=13 4237 (2907-41 975)	0.335
BNP (pmol/L)	N=381 1187 (367-2941)	N=346 1190 (367-2941)	N=35 1173 (529-3017)	0.975	N=24 777 (188-1509)	N=11 2311 (1055-5173)	0.008

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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%)	0.630	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
- 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
Hemorrhagic 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%)	0.370	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%)	0.250	184/212 (86.8%)	37/55 (67.3%)	<0.001

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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
Streptococcus viridans	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
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

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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 12.0 (8.0-18.0)	N=1755 12.0 (8.0-18.0)	N=137 11.0 (7.0-17.0)	0.034	N=110 11.0 (7.0-16.0)	N=27 12.0 (8.0-18.0)	0.549
Abscess	323/3108 (10.4%)	286/2835 (10.1%)	36/266 (13.5%)	0.200	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

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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 38 (30-50)	N=1593 38 (30-50)	N=175 35 (28-48)	0.397	N=137 35 (28-45)	N=38 37 (26-60)	0.193
LVEF (%)	N=2657 58 (50-64)	N=2428 58 (50-65)	N=222 55 (50-62)	0.240	N=173 56 (50-65)	N=49 55 (50-60)	0.021

BNP, B-type natriuretic peptide; CoNS, coagulase-negative staphylococcus; 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; PM, pacemaker.

Table 2: In-hospital and follow-up events

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
Complications despite 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
- 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
Hemorrhagic 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

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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	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
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
Hemodynamic 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

Variable	Total n=3113	First IE episode n=2839 (91.4%)	Recurrent IE n=267 (8.6%)	P-value (first IE episode vs recurrent IE)	Reinfection n=212 (79.4%)	Relapse n=55 (20.6%)	P-value (reinfection vs relapse)
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

IE, infective endocarditis.

Table 3: Multivariate Cox proportional hazard models performed in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE) as a predictor of in-hospital mortality [cut-off used at 30 days, inclusion date as reference and with the IE group (recurrent/non-recurrent IE) as fixed covariable]

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P-value Global	Modality	HR (95% CI)	P-value
504/504	Stat=16.19 with 9DF and 10 groups. P=0.063	0.8212	Recurrent IE vs. first IE episode	0.015	Recurrent IE	0.17 (0.04-0.71)	0.015
			Severe valvular regurgitation	<0.001	Yes vs. No	45.20 (4.72-432.76)	<0.001
			Cardiac surgery	0.037	Indication - not performed	7.25 (1.60-32.95)	0.010
					No indication	2.24 (0.54-9.38)	0.269
			Complications despite therapy - Septic shock	0.002	Yes vs. No	54.87 (4.27-705.78)	0.002
			Methi-S Staphylococcus aureus	0.001	Yes vs. No	41.80 (4.50-388.74)	0.001

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P-value Global	Modality	HR (95% CI)	P-value
			Heart failure	0.007	Yes vs. No	7.35 (1.74-31.13)	0.007
			Mechanical mitral valve	0.004	Yes vs. No	223.5 (5.5-9068.3)	0.004

CI, confidence interval; DF, degree of freedom; HR, hazard ratio; Methi-S, methicillin-sensitive.

Table 4: 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 9DF and 10 groups. P=0.061	0.8366	IE relapse vs. reinfection	0.919	IE relapse vs. reinfection	0.95 (0.34-2.68)	0.919
			Severe valvular regurgitation	0.013	Yes vs. No	3.14 (1.27-7.76)	0.013
			Cardiac surgery	0.027	Indication - not performed	6.26 (1.61-24.38)	0.008
					No indication	3.58 (0.81-15.75)	0.092
			Complications despite therapy - Septic shock	<0.001	Yes vs. No	6.70 (2.73-16.43)	<0.001
			Clinical examination - Cardiogenic shock	0.009	Yes vs. No	18.34 (2.10-160.53)	0.009

CI, confidence interval; DF, degree of freedom; HR, hazard ratio; IE, infective endocarditis.

Table 5: Multivariable Cox proportional hazard models performed in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE) as a predictor of 1-year mortality [cut-off used at 365 days, inclusion date as reference and with the IE group (recurrent/non-recurrent IE) as fixed covariable]

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P-value Global	Modality	HR (95% CI)	P-value
504/504	Stat=63.86 with 9DF and 10 groups. P<0.001	0.7550	Recurrent IE vs. first IE episode	0.871	Recurrent IE	0.96 (0.60-1.55)	0.871
			Cardiac surgery	0.018	Indication - not performed	2.79 (1.34-5.81)	0.006
					No indication	1.30 (0.65-2.63)	0.459
			Complications despite therapy - CHF	<0.001	Yes vs. No	4.31 (1.97-9.45)	<0.001
			Complications despite therapy - Septic shock	0.005	Yes vs. No	3.31 (1.43-7.71)	0.005

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P-value Global	Modality	HR (95% CI)	P-value
			Methi-S Staphylococcus aureus	0.002	Yes vs. No	3.47 (1.57-7.65)	0.002
			Chronic renal failure	0.021	Yes vs. No	2.18 (1.13-4.21)	0.021

CHF, congestive heart failure; CI, confidence interval; DF, degree of freedom; HR, hazard ratio; Methi-S, methicillin-sensitive.

Table 6: Multivariate Cox proportional hazard models performed in patients with relapse and reinfection as a predictor of 1-year mortality (cut-off used at 365 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
233/267	Stat=5.17 with 8DF and 10 groups. P=0.740	0.7579	IE relapse vs reinfection	0.954	IE relapse vs reinfection	1.02 (0.54-1.93)	0.954
			Clinical examination - NYHA class III and IV	0.002	Yes vs. No	2.60 (1.44-4.71)	0.002
			Cardiac surgery	0.003	Indication - not performed	3.12 (1.60-6.08)	<0.001
					No indication	1.50 (0.70-3.23)	0.294
			Complications despite therapy - Embolic events	0.002	Yes vs. No	2.58 (1.43-4.66)	0.002
			Complications despite therapy - Septic shock	<0.001	Yes vs. No	4.51 (2.44-8.35)	<0.001

Sample size	Overall goodness-of-fit test	Concordance statistic	Covariate	P-value Global	Modality	HR (95% CI)	P-value
			Clinical examination - Cardiogenic shock	<0.001	Yes vs. No	14.98 (3.25-68.93)	<0.001

CI, confidence interval; DF, degree of freedom; HR, hazard ratio; IE, infective endocarditis; NYHA, New York Heart Association.

Figure 1: Flow-chart study design

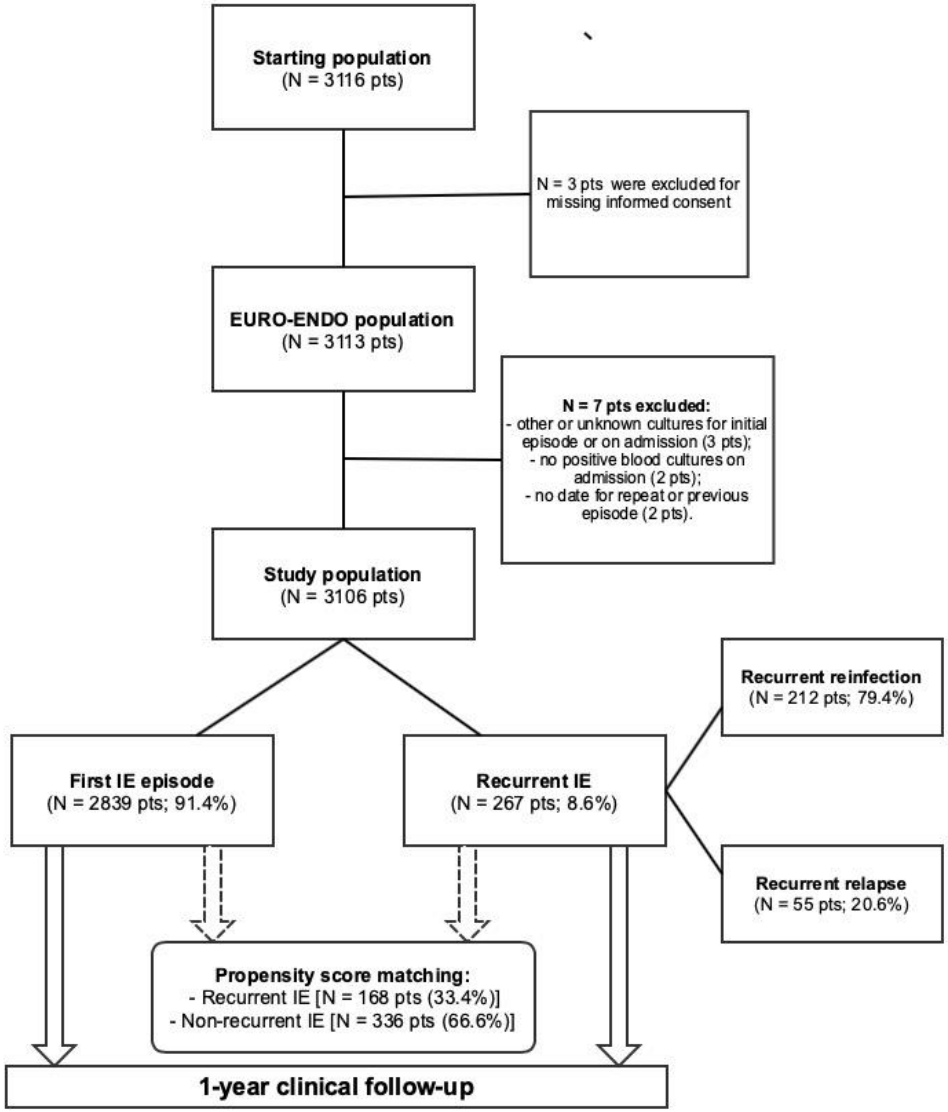


Figure 2: Kaplan-Meier survival curves during hospitalization in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE)

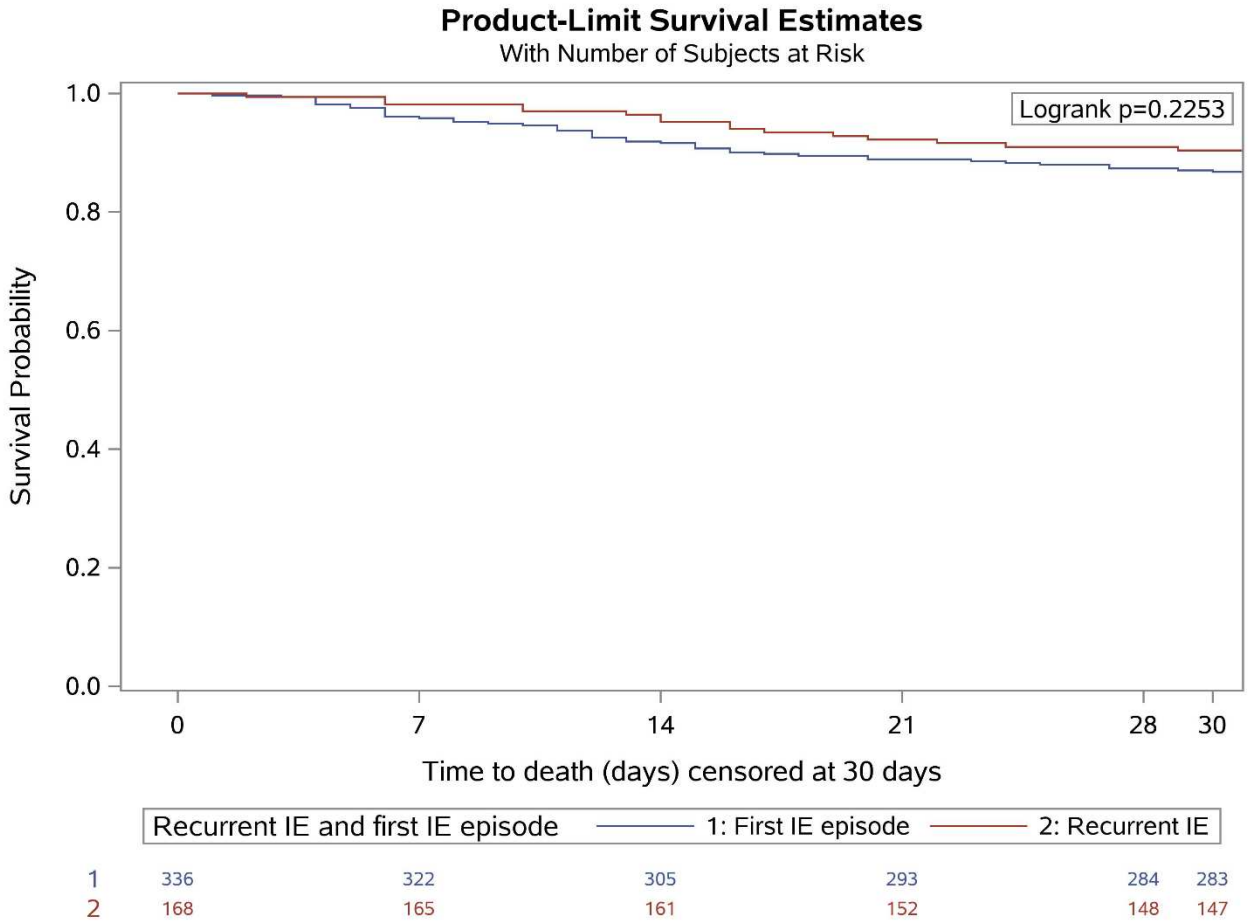
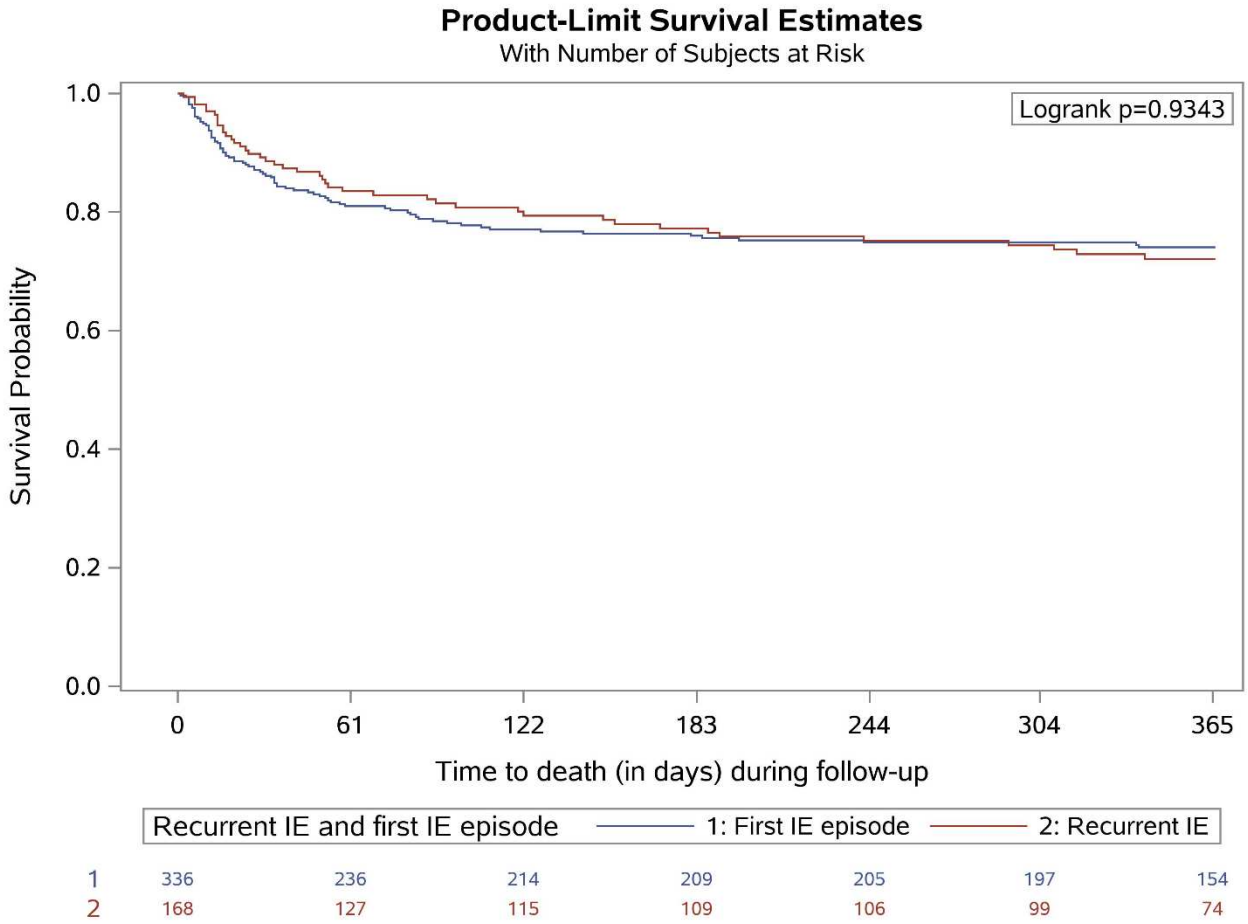


Figure 3: Kaplan-Meier survival curves at 1-year follow-up in the matched cohort of patients with recurrent and non-recurrent infective endocarditis (IE)



Supplementary Table 1: Distribution of the study population

Variable	Modality	Total n=3113	ESC countries n=2470 (79.3%)	Non-ESC countries n=643 (20.7%)
Recurrent IE and first-episode IE	Recurrent IE	267/3106 (8.6%)	214/2463 (8.7%)	53/643 (8.2%)
	First-episode IE	2839/3106 (91.4%)	2249/2463 (91.3%)	590/643 (91.8%)
Recurrent IE group	Relapse	55/267 (20.6%)	45/214 (21.0%)	10/53 (18.9%)
	Reinfection	212/267(79.4%)	169/214 (79.0%)	43/53 (81.1%)
Type of IE recurrence	Recurrent IE in IVDAs	35/3057 (1.1%)	32/2418 (1.3%)	3/639 (0.5%)
	Recurrent IE in non-IVDA	230/3057 (7.5%)	180/2418 (7.4%)	50/639 (7.8%)
	First-episode IE in IVDAs	177/3057 (5.8%)	149/2418 (6.2%)	28/639 (4.4%)

Variable	Modality	Total n=3113	ESC countries n=2470 (79.3%)	Non-ESC countries n=643 (20.7%)
	First-episode IE in non- IVDA	2615/3057 (85.5%)	2057/2418 (84.1%)	558/639 (87.3%)

ESC, European Society of Cardiology; IE, infective endocarditis; IVDA, intravenous drug abuser;

Supplementary Table 2: Comparison of recurrent infective endocarditis (IE) in intravenous drug abusers (IVDAs) vs non-IVDAs and vs IVDAs with a first episode of IE

Variable		Recurrent IE in IVDAs n=35 (13.2%)	Recurrent IE in non-IVDAs n=230 (86.8%)	First-episode IE in IVDAs n=177 (83.5%)	P-value (recurrent IE in IVDAs vs non-IVDAs)	P-value (recurrent IE vs first-episode IE in IVDAs)
Male sex		29 (82.9%)	169 (73.5%)	143 (80.8%)	0.234	0.775
Age (years)		36.5 (±8.7)	61.6 (±16.2)	37.0 (±11.3)	<0.001	0.865
		35.0 (28.0-45.0)	64.0 (54.0-73.0)	35.0 (30.0-43.0)	<0.001	0.865
Medical history						
Heart failure		9 (30.0%)	69 (34.3%)	10 (5.8%)	0.640	<0.001
Congenital heart disease		3 (8.6%)	29 (12.6%)	9 (5.1%)	0.780	0.423
Pacemaker		3 (8.6%)	30 (13.0%)	3 (1.7%)	0.455	0.025
Valvular intervention		18 (51.4%)	164 (71.3%)	2 (1.1%)	0.018	<0.001
Invasive intervention in the last 6 months						
Colonoscopy		0 (0.0%)	12 (6.2%)	0 (0.0%)	0.373	NA
Dental procedure		1 (3.0%)	18 (8.3%)	2 (1.2%)	0.483	0.413
Neuro-intervention		0 (0.0%)	1 (0.5%)	0 (0.0%)	1.000	NA

Clinical conditions					
Arterial hypertension	2 (5.7%)	123 (53.7%)	11 (6.2%)	<0.001	1.000
Chronic renal failure	1 (2.9%)	52 (22.6%)	8 (4.5%)	0.006	1.000
Dialysis	0 (0.0%)	15 (6.5%)	4 (2.3%)	0.232	1.000
Diabetes mellitus	1 (2.9%)	50 (21.8%)	4 (2.3%)	0.008	1.000
Alcohol abuse	10 (35.7%)	18 (8.0%)	41 (25.0%)	<0.001	0.235
Intravenous catheter	2 (5.7%)	18 (7.8%)	12 (6.8%)	1.000	1.000
Charlson comorbidity index	1.0 (0.0-3.0)	4.0 (2.0-5.0)	1.0 (0.0-2.0)	<0.001	0.222
Time since first symptoms (days)	13.5 (5.5-32.5)	8.0 (2.0-30.0)	15.0 (6.0-38.0)	0.109	0.734
Complications at admission					
Congestive heart failure	8 (22.9%)	50 (21.7%)	43 (24.3%)	0.882	0.856
Spondylitis	4 (11.4%)	7 (3.0%)	8 (4.5%)	0.043	0.116
Embolic events	15 (42.9%)	42 (18.3%)	93 (52.5%)	<0.001	0.295
- Cerebral	0 (0.0%)	22 (9.6%)	16 (9.0%)	0.091	0.080

- Pulmonary	12 (34.3%)	8 (3.5%)	71 (40.1%)	<0.001	0.519
- Splenic	1 (2.9%)	8 (3.5%)	6 (3.4%)	1.000	1.000
- Renal	0 (0.0%)	2 (0.9%)	5 (2.8%)	1.000	0.593
- Peripheral	3 (8.6%)	9(3.9%)	6 (3.4%)	0.201	0.171
- Other	0 (0.0%)	2 (0.9%)	4 (2.3%)	1.000	1.000
Hemorrhagic stroke	0 (0.0%)	5 (2.2%)	3 (1.7%)	1.000	1.000
Microbiological findings					
Positive blood culture	32(91.4%)	187 (81.3%)	140 (79.1%)	0.141	0.088
Staphylococcus aureus	16 (45.7%)	55 (23.9%)	90 (50.8%)	0.007	0.579
Coagulase-negative staphylococci	0 (0.0%)	20 (8.7%)	14 (7.9%)	0.070	0.085
Streptococcus viridans	2 (5.7%)	19 (8.3%)	7 (4.0%)	1.000	0.645
Enterococcus	8 (22.9%)	41 (17.8%)	15 (8.5%)	0.475	0.031
Streptococcus bovis (gallolyticus)	1 (2.9%)	10 (4.3%)	1 (0.6%)	1.000	0.304

Gram-negative bacillus	0 (0.0%)	4 (1.7%)	4 (2.3%)	1.000	1.000
Echocardiographic findings					
Aortic	10 (28.6%)	95 (41.5%)	40 (22.6%)	0.146	0.447
Mitral	6 (17.1%)	102 (44.5%)	40 (22.6%)	0.002	0.474
Tricuspid	26 (74.3%)	27 (11.8%)	111 (62.7%)	<0.001	0.191
Pulmonary	2 (5.7%)	7 (3.1%)	5 (2.8%)	0.340	0.326
ICD/PM/other	1 (2.9%)	17 (7.4%)	1 (0.6%)	0.482	0.304
Vegetation maximal length	18.0 (11.0-25.0)	11.0 (7.0-15.0)	16.0 (11.0-22.0)	<0.001	0.619
Abscess	4 (11.4%)	32 (14.0%)	10 (5.6%)	0.797	0.256
Pseudoaneurysm	2 (5.7%)	11 (4.8%)	0 (0.0%)	0.685	0.027
Fistula	2 (5.7%)	5 (2.2%)	1 (0.6%)	0.234	0.071
Paraprosthetic regurgitation	5 (14.3%)	34 (14.8%)	1 (0.6%)	0.931	<0.001
New prosthetic dehiscence	2 (5.7%)	23 (10.0%)	0 (0.0%)	0.548	0.027
Severe regurgitation	19 (54.3%)	59 (25.8%)	98 (55.4%)	<0.001	0.906

Severe stenosis	3 (8.6%)	15 (6.6%)	4 (2.3%)	0.716	0.090
Perforation	2 (5.7%)	17 (7.4%)	19 (10.7%)	1.000	0.539
Right ventricular dysfunction	9 (30.0%)	38 (19.0%)	27 (15.7%)	0.164	0.059
LVEF (%)	56.0 (55.0-65.0)	55.0 (50.0-60.0)	60.0 (55.0-67.0)	0.189	0.072
Complications under therapy					
Embolic events	11 (31.4%)	47 (20.4%)	63 (35.6%)	0.143	0.637
- Pulmonary	10 (28.6%)	7 (3.0%)	47 (26.6%)	<0.001	0.806
- Cerebral	0 (0.0%)	25 (10.9%)	11 (6.2%)	0.055	0.218
- Spleen	1 (2.9%)	11 (4.8%)	5 (2.8%)	1.000	1.000
- Renal	1 (2.9%)	6 (2.6%)	4 (2.3%)	1.000	1.000
- Hepatic	0 (0.0%)	1 (0.4%)	1 (0.6%)	1.000	1.000
- Other	0 (0.0%)	4 (1.7%)	3 (1.7%)	1.000	1.000
Hemorrhagic stroke	0 (0.0%)	5 (2.2%)	2 (1.1%)	1.000	1.000

Spondylitis	2 (5.7%)	6 (2.6%)	8 (4.5%)	0.286	0.672
Congestive heart failure	5 (14.3%)	35 (15.2%)	22 (12.4%)	0.886	0.782
Cardiogenic shock	3 (10.0%)	15 (7.5%)	9 (5.2%)	0.712	0.393
Septic shock	8 (22.9%)	20 (8.7%)	27 (15.3%)	0.018	0.268
Acute renal failure	3 (8.6%)	36 (15.7%)	28 (15.8%)	0.271	0.267
Persistent fever	9 (30.0%)	20 (10.0%)	35 (20.3%)	0.005	0.237
Increasing vegetation size	6 (17.1%)	16 (7.0%)	23 (13.0%)	0.053	0.589
New abscess	4 (11.4%)	15 (6.5%)	10 (5.6%)	0.292	0.256
EuroSCORE	6.1 (1.9-8.1)	8.0 (3.8-19.8)	1.7 (1.2-3.7)	0.010	<0.001
Theoretical indication for surgery/procedure	24 (68.6%)	156 (67.8%)	115 (65.0%)	0.930	0.682
Indication - Hemodynamic	10 (28.6%)	66 (28.7%)	57 (32.2%)	0.988	0.673
Indication - Embolic	10 (28.6%)	43 (18.7%)	55 (31.1%)	0.174	0.769
Indication - Infectious	21 (60.0%)	105 (45.7%)	77 (43.5%)	0.113	0.074
Surgery performed	12 (50.0%)	105 (67.3%)	77 (67.0%)	0.098	0.115

In-hospital death	9 (25.7%)	39 (17.0%)	20 (11.3%)	0.210	0.032
Events at follow-up					
1-year mortality	3/21 (14.3%)	21/163 (12.9%)	9/111 (8.1%)	0.741	0.405
1-year IE recurrence	2/13 (15.4%)	12/120 (10.0%)	14/87 (16.1%)	0.628	1.000
Congestive heart failure	4/16 (25.0%)	36/127 (28.3%)	14/86 (16.3%)	1.000	0.475
Surgery	1/18 (5.6%)	16/142 (11.3%)	16/90 (17.8%)	0.696	0.295

ICD, implantable cardioverter-defibrillator; IE, infective endocarditis; IVDA, intravenous drug abuser; LVEF, left ventricular ejection fraction; PM, pacemaker.

Supplementary Table 3: Baseline covariates after propensity score matching with standardized differences

Variable	Total N=504	Recurrent IE N=168 (33.33%)	Non-recurrent IE N=336 (66.67%)	SD
Calculated age	58.2 (±18.7)	58.1 (±17.6)	58.3 (±19.3)	0.01
Male sex	365 (72.4%)	121 (72.0%)	244 (72.6%)	0.01
Location of endocarditis				
Aortic valve	245(48.6%)	82(48.8%)	163(48.5%)	0.01
Mitral valve	210(41.7)	74(44.0%)	136(40.5%)	0.07
Tricuspid valve	71(14.1%)	24(14.3%)	47(14.0%)	0.01
Pulmonary valve	30(6.0%)	8(4.8%)	22(6.5%)	0.08
ICD/PM	55(10.9%)	17(10.1%)	38(11.3%)	0.04
Clinical data				
Prosthetic + repair valve	313 (62.1%)	10260.7%)	211(62.8%)	0.04
History Intravenous drug dependency	47 (9.3%)	15(8.9%)	32(9.5%)	0.02
History of congestive Heart failure	160(31.7%)	50(29.8%)	110 (32.7%)	0.06
Diabetes mellitus	114(22.6%)	37(22.0%)	77 (22.9%)	0.02
Arterial hypertension	268(53.2%)	87(51.8%)	181(53.9%)	0.04
COPD/asthma	46(9.1%)	14(8.3%)	32(9.5%)	0.04
Chronic renal failure	128(25.4%)	41(24.4%)	87 (25.9%)	0.03
Time since first symptoms (days)	15.0(4.0 ;35.0)	12.0(3.0 ;32.5)	15.5(5.0 ;36.5)	0.05
Microbiological findings				
Staphylococcus Aureus	108(21.4%)	36 (21.4%)	72 (21.4%)	0.00
Enterococcus	110 (21.8%)	33 (19.6%)	77 (22.9%)	0.08
Echocardiographic findings				
Vegetation	330(65.5%)	114(67.9%)	216 (64.3%)	0.08
Abscess	61(12.1%)	22 (13.1%)	39 (11.6%)	0.05
Pseudoaneurysm	21(4.2%)	8(4.8%)	13(3.9%)	0.04
Severe regurgitation	147(29.2%)	55(32.7%)	92(27.4%)	0.12

Severe stenosis	34(6.7%)	12(7.1%)	22(6.5%)	0.02
LVEF (%)	55.0 (50.0;62.0)	55.0 (50.0;60.5)	56.0 (50.0;62.0)	0.01
Complications despite therapy				
Embolic events	102(20.2%)	35(20.8%)	67(19.9%)	0.02
Hemorrhagic stroke	8(1.6%)	3(1.8%)	5(1.5%)	0.02

SD : standard differences

All these covariates were used for the propensity score matching between recurrent IE and non-recurrent IE.

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The graphical abstract should clearly summarize the focus and findings of the article, and will be published as part of the article online and in PDF. This can be one of the key images/figures/graphs of the article. The graphical abstract should be submitted for peer review as a separate file, selecting the appropriate file-type designation in the journal's online submission system.
The file should be clearly named, e.g. *graphical_abstract.tiff*, *video_abstract.mp4*. Guidance on appropriate file format and resolution for graphics is available. Please ensure graphical abstracts are in landscape format.
*Graphical abstracts have now replaced the 'take-home figure'

'One-sentence Summary': short non-technical summary stating the novelty of the article in simple language. Please use the third person, not first person (i.e. do not use 'I' or 'we').