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Outcomes of infective endocarditis in the current era: Early predictors of a poor prognosis

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ABSTRACT

Background: The early identification of patients at risk of complications of infective endocarditis (IE) using parameters obtained as part of routine practice is essential for guiding clinical decision-making. This study aimed to identify a parameter at hospital admission that predicts the outcome, adding value to other well-known factors of a poor prognosis in IE.
Methods: Two hundred and three patients with IE were included in this study. Clinical evaluation, echocardiography, blood cultures, and routine laboratory tests were performed at hospital admission. The endpoint was in-hospital mortality.
Results: The mean age of the patients was 48.2 ± 16.6 years; 62% were male and 38% had rheumatic heart disease. During treatment, cardiac surgery was performed in 111 patients (55%), and the overall in-hospital mortality rate was 32%. In the multivariable analysis, the independent predictors of death were age (odds ratio (OR) 1.07, 95% confidence interval (CI) 1.02–1.13), C-reactive protein (CRP) at hospital admission (OR 1.12, 95% CI 1.04–1.21), length of the vegetation at diagnosis (OR 1.15, 95% CI 1.03–1.28), development of heart failure (OR 6.43, 95% CI 2.14–19.33), and embolic events during antimicrobial therapy (OR 12.14, 95% CI 2.11–71.89).
Conclusions: An elevated CRP level at hospital admission and vegetation length at diagnosis were strong predictors of in-hospital mortality in IE, independent of other prognostic parameters, specifically taking into account patient characteristics and complications during therapy.

Introduction

Infective endocarditis (IE) is a serious clinical condition that is still responsible for a substantial mortality rate, even with appropriate management in accordance with current guidelines (Habib et al., 2015; Baddour et al., 2015). The treatment of IE has improved in recent decades, with an early surgical approach to prevent valvular structural damage and systemic embolism, which are associated with a poor prognosis (Baddour et al., 2015; Thuny et al., 2011; Hasbun et al., 2003; Vikram et al., 2003). However, the in-hospital mortality rate of patients with IE remains unchanged, ranging from 15% to 30% (Leone et al., 2012; Murdoch et al., 2009; Nadji et al., 2009; Olmos et al., 2013; Nunes et al., 2010; Chu et al., 2004). There are several reasons for these high mortality rates, including changes in the population at risk, disease presentation, and virulence of the infecting microorganism (Cahill and Prendergast, 2016; Wallace et al., 2002).

There is growing recognition that IE is not a single disease, but rather encompasses a wide spectrum of disease presentations depending on several conditions. Due to this complexity, the management of patients with IE should be conducted in reference

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centers by a specialized team (the 'endocarditis team') (Habib et al., 2015; Cahill and Prendergast, 2016). This multidisciplinary approach is crucial to improve the prognosis of this disease. Nevertheless, the delivery of high-level coordinated care remains difficult, even in healthcare systems in high-income countries (Cahill and Prendergast, 2016). In developing countries with limited resources, prompt diagnosis remains a key point for improving clinical outcomes (Chu et al., 2015). Although new imaging techniques have been used increasingly to improve the diagnosis of IE, they are not always available in low-income countries (Habib et al., 2015). Therefore, the early identification of patients at risk of complications of IE using parameters obtained as part of routine practice could be an essential tool for guiding clinical decision-making.

This prospective cohort study was designed to determine the predictors of in-hospital mortality in a large population of patients with IE in the contemporary era of a more aggressive approach to microbial eradication. In particular, the aim was to identify a parameter at hospital admission that could be a useful predictor of the outcome, adding value to other well-known factors of a poor prognosis in IE.

Methods

Study population

A total of 203 consecutive patients admitted to a single tertiary care hospital between September 2005 and April 2017 with definite or possible IE based on the modified Duke criteria (Li et al., 2000) were prospectively included in the study.

This study was approved by the institutional ethics committee; written informed consent was obtained from all patients. Clinical evaluations, echocardiography, blood cultures, and routine laboratory tests were performed within the first 72 h of admission. For the participants who presented repeated episodes of IE, only the first episode was included.

Clinical and laboratory data

Patient information was recorded, including the duration of symptoms, temperature course, vascular and other immunological phenomena, administration of antibiotics, predisposing cardiac conditions, and comorbidities. Routine laboratory tests and blood cultures were performed at the time of hospital admission and during treatment. Routine laboratory investigations recorded were the complete blood count, C-reactive protein (CRP) level, serum chemistry, and urine analysis. CRP was measured by conventional assay.

All patients underwent transthoracic (TTE) and/or transesophageal echocardiography (TEE), as clinically indicated (Habib et al., 2015, 2010). The presence of a vegetation, abscess, new dehiscence of a prosthetic valve, or new valvular regurgitation was considered a major modified Duke criterion for IE (Li et al., 2000). Measurements of the vegetation length were performed in various planes, and the maximum length was selected. Abscess was defined as a thickened area or mass with a heterogeneous echogenic or echolucent appearance (Habib et al., 2010). In order to determine the severity of the valvular regurgitation, a semiquantitative analysis was performed using color flow Doppler echocardiography. Additionally, information regarding the mechanism and hemodynamic severity of the valve lesion and an assessment of the underlying ventricular function were obtained.

Endpoint definitions

The primary endpoint was in-hospital death due to any complication related to IE or its medical or surgical treatment. Early surgery was defined as the replacement or repair of the affected valve during the course of antibiotic therapy for IE. The main indications for surgery were severe heart failure, embolic event, persistent bacteremia, paravalvular complication, and severe valvular regurgitation. Vegetation size and infecting microorganism were not criteria to indicate surgery, unless

Table 1
Baseline clinical characteristics of the patients according to in-hospital mortality.[a]

Baseline characteristics	Survived ($n = 138$)	Died ($n = 65$)	p-Value
Age (years)	47 (32–61)	52 (41–63)	0.060
Sex, male	86 (62%)	39 (60%)	0.751
Time from initial manifestation to diagnosis (days)	14 (7–54)	14 (4–28)	0.199
Predisposing conditions			
Previous IE	12 (9%)	8 (12%)	0.398
Rheumatic heart disease	54 (39%)	24 (37%)	0.841
Prosthetic valves	39 (28%)	16 (25%)	0.448
Endocavitary devices (pacemaker/ICD)	39 (28%)	14 (22%)	0.338
Diabetes mellitus	11 (8%)	14 (21%)	0.011
Renal insufficiency in hemodialysis	20 (14%)	8 (12%)	0.726
Central IV access	11 (8%)	15 (23%)	0.002
Neurological manifestations	24 (17%)	13 (20%)	0.517
Embolic events	14 (10%)	15 (23%)	0.025
Laboratory findings			
Hemoglobin (g/dl)	10.0 (8.8–11.3)	9.6 (8.4–11.0)	0.066
Leukocytes (cells $\times 10^9$/l)	10.9 (7.9–15.4)	13.7 (10.1–18.7)	0.008
CRP (mg/l)	60 (32–136)	114 (72–251)	<0.001
Main causative microorganisms			
Staphylococcus aureus	19 (14%)	18 (28%)	0.015
CoNS	23 (17%)	9 (14%)	0.419
Streptococci	23 (17%)	6 (9%)	0.116
Enterococcus species	10 (7%)	5 (8%)	0.986
Negative culture findings	51 (37%)	17 (26%)	0.127

IE, infective endocarditis; ICD, implantable cardioverter defibrillator; IV, intravenous; CRP, C-reactive protein; CoNS, coagulase-negative Staphylococcus.
[a] Data are expressed as the median (interquartile range), or absolute number (percentage).

associated with complications. Adverse events were collected at the time of hospital admission and during treatment until discharge from the hospital.

Statistical analysis

Baseline characteristics were summarized as the median value with interquartile range for continuous variables and as the frequency with proportion for categorical variables. Differences between patients who survived and those who died were compared using the Chi-square test or Fisher's exact test for categorical variables and with the Mann–Whitney *U*-test for continuous variables.

Logistic regression analysis was performed to determine the characteristics that were independently associated with in-hospital death. Baseline clinical, echocardiographic, and microbiological variables were tested as potential predictors of in-hospital mortality. Clinical, microbiological, and echocardiographic variables that were found to be significantly associated with death in the univariable analysis were included in the multivariable logistic regression model. The association between the causative microorganism and mortality was tested by comparing the patients infected with *Staphylococcus aureus* with a group including all other microbiological causes and culture-negative IE cases.

Calibration of the multivariable model was assessed by a goodness-of-fit test, and discrimination was measured by the area under the receiver operating characteristics (ROC) curve, or *c* statistic. To compare the accuracy of the model with and without CRP levels at admission, the area under the ROC curve (AUC) was calculated. All analyses were performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

The overall clinical characteristics of the patients stratified according to in-hospital mortality are shown in Table 1. A total of 195 (95%) patients had definite IE according to the modified Duke criteria, and 11 (5%) met the criteria for possible IE. The mean age of the patients was 48 ± 17 years (range 14–84 years); 125 patients were male (62%), giving a male to female ratio of 1.6:1. The median time between the onset of symptoms and the diagnosis of IE was 14 days (interquartile range 7–33 days; total range 1–224 days).

A previous history of IE was observed in 10% of the patients, and rheumatic heart disease was a predisposing condition in 38% of the cases. The major initial symptoms were fever (80%), weight loss (52%), night sweats (34%), and myalgia (18%). Physical examination revealed a cardiac murmur in 75% and splenomegaly in 14%. Embolic events were detected in 14% of the patients at the diagnosis of IE. Neurological manifestations were found in 42 patients (21%), including ischemic stroke in 13% and cerebral bleeding in 4%.

The classic signs that are often considered diagnostic of IE such as Janeway lesions (5.1%), Osler's nodes (2.6%), splinter hemorrhages (5.4%), and conjunctival petechiae (4.4%) were uncommon and observed only in patients with long-lasting disease. Routine laboratory investigations showed anemia in 84% of the patients with elevated CRP.

Blood culture-negative IE occurred in 68 patients (33.5%) and microorganisms were isolated from 135 individuals (66.5%). The most frequent causative microorganisms isolated were staphylococci (69 patients, 51.1%), with *S. aureus* accounting for 27.4% of all cases of blood culture-positive IE. Streptococci were isolated in 21.5% of the cases and enterococci in 11.1%. Other microorganisms were isolated in 22 patients (16.3%), including Gram-positive pathogens, HACEK organisms (*Haemophilus spp*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), and fungi.

TEE was performed in 77.2% of the patients, whereas TTE alone was used for the diagnosis of IE in 22.8%. The left-sided native valve was affected in 55.7%, while prosthetic valve IE was diagnosed in 55 patients (27.1%). The remaining 44 patients (21.6%) had right-sided IE, mainly pacemaker-related IE.

Complications and outcomes

Echocardiography findings, complications, and outcomes during the treatment are presented in Table 2. Vegetations were detected in 88.2% of the cases, and the length of these vegetations was associated with mortality. Valvular regurgitation as a result of leaflet rupture or perforation was found in 17.3% and perivalvular abscess at diagnosis in 6.4%. A prosthetic valve complication including dehiscence or new paravalvular regurgitation was observed in 7.4%.

Table 2
Echocardiography findings, complications, and outcomes stratified by in-hospital mortality.[a]

	Survived (n = 138)	Died (n = 65)	p-Value
Echocardiography features			
LV end-diastolic diameter (mm)	53.2 ± 12.8	56.5 ± 8.2	0.302
LV end-systolic diameter (mm)	35.7 ± 11.6	39.1 ± 10.4	0.294
LV ejection fraction (%)	56.2 ± 19.2	56.5 ± 14.4	0.953
Systolic pulmonary artery pressure (mmHg)	40.9 ± 16.2	41.4 ± 8.3	0.909
Vegetation length (mm)	11 (8–15)	15 (9–19)	0.021
Vegetation extent[b]	24 (17%)	17 (26%)	0.112
Vegetation valve			
Aortic	26 (19%)	17 (26%)	0.201
Mitral	49 (36%)	21 (32%)	
Abscess, dehiscence, or new regurgitation	38 (28%)	21 (32%)	0.295
Complications			
Severe heart failure	40 (29%)	39 (60%)	<0.001
New embolic events	8 (6%)	14 (22%)	0.002
Cerebrovascular complications	13 (9%)	14 (22%)	0.013
Persistent bacteremia	18 (13%)	15 (23%)	0.032
Cardiac surgery	79 (57%)	32 (49%)	0.335

LV, left ventricle.
[a] Data are expressed as the mean value ± standard deviation, median (interquartile range), or absolute number (percentage).
[b] Single vegetation versus multiple vegetations in a single leaflet or in more than one leaflet.

In the overall patient population, heart failure was diagnosed in 138 patients (68%); 79 of them developed heart failure during the treatment of IE. Cardiac surgery was performed in 111 patients (55%), mainly due to severe valvular dysfunction with heart failure (27%) and also to persistent bacteremia despite antibiotic treatment (15%). New embolic events were diagnosed in 11%. Patients with device-associated IE had the device removed after a week of antibiotic treatment. Neurological complications were observed in 14% of the patients and prolonged fever was found in 16%.

Predictors of in-hospital mortality

The median duration of hospital stay was 42 days, ranging from 1 to 179 days. During this period, 65 patients died, corresponding to an overall mortality rate of 32%. The leading causes of IE-related death were severe heart failure, septic shock, and cerebrovascular complications. Table 3 presents the factors associated with overall in-hospital mortality in the univariable analysis.

Several factors were associated with in-hospital mortality, including diabetes mellitus and chronic intravenous access. The inflammatory markers of disease severity, especially high white blood cell count and CRP level, were predictors of death. Similarly, *S. aureus* as the causative microorganism and large dimensions of the vegetation were also associated with a poor prognosis (Table 3). The complications during treatment associated with death were heart failure, new embolism (other than stroke), neurological complications, and uncontrolled infection.

Multivariable logistic regression revealed that age, CRP level at hospital admission, and length of the vegetation at IE diagnosis were associated with death (Table 4). Additionally, during appropriate antimicrobial therapy the development of severe heart failure and occurrence of embolic events were also independent predictors of in-hospital mortality. The goodness-of-fit of the multivariable model was determined by Hosmer–Lemeshow test (Chi-square = 9.654, $p = 0.290$). The *c* statistic of the model including CRP was 0.90 (95% confidence interval 0.82–0.98). Of note, a high CRP level at admission was a strong predictor of death, regardless of other complications during treatment or the etiological agent of the IE. *S. aureus* infection was associated with new heart failure and high CRP levels, but did not remain an independent predictor of death in the model including these variables.

Table 3
Univariate predictors of in-hospital mortality.

Variables	OR	95% CI	*p*-Value
At diagnosis			
Age (years)	1.018	0.999–1.036	0.062
Diabetes mellitus	2.978	1.251–7.089	0.014
Central IV access	3.580	1.536–8.342	0.003
Embolic event	2.674	1.179–6.069	0.019
Hemoglobin (g/dl)	0.839	0.710–0.990	0.038
CRP (mg/l)[a]	1.005	1.002–1.008	0.001
Leukocytes[b] (cells × 10^9/l)	1.054	1.015–1.094	0.006
Staphylococcus aureus	2.553	1.224–5.326	0.012
Vegetation length (mm)	1.070	1.013–1.131	0.016
During treatment			
Heart failure[c]	3.537	2.017–6.202	<0.001
New embolic events	4.744	1.865–12.067	0.001
Neurological complications	2.888	1.259–6.627	0.012
Persistent bacteremia	2.265	1.041–4.928	0.039

OR, odds ratio; CI, confidence interval; IV, intravenous; CRP, C-reactive protein.
[a] Serum level at admission.
[b] OR per 10^9/l of leukocytes.
[c] New or worsening heart failure after the diagnosis of infective endocarditis, during treatment.

Discussion

IE is a heterogeneous disease with a variable clinical presentation and prognosis, depending basically on the underlying cardiac condition, infecting microorganism, patient characteristics, and development of complications (Cahill and Prendergast, 2016; Lauridsen et al., 2015). Despite improvements in its diagnosis and therapeutic management, IE continues to be associated with high mortality and major morbidity (Murdoch et al., 2009; Wallace et al., 2002; Chu et al., 2015). This study evaluated several factors that influence the outcome of IE. The value of CRP at admission was specifically investigated as a predictor of subsequent death during hospitalization in this large population of patients with IE.

The large cohort included is representative of the spectrum of the disease often seen in developing countries in the current era of improved medical care (Chu et al., 2015). The results showed that CRP at admission strongly predicts in-hospital death, independent of age, heart failure, embolic event, and size of the vegetation. The CRP level early in the course of IE predicts patients who will die despite appropriate management of their disease.

The pattern of IE varies worldwide, especially related to patient characteristics and predisposing conditions. In low-income countries, rheumatic heart disease remains the most common underlying valvular condition, whereas degenerative valve disease is the most frequent native valve predisposing factor in high-income countries (Nunes et al., 2010; Cahill and Prendergast, 2016). In recent decades, the epidemiological profile of IE has changed substantially around the world, with a progressive increase in age of the affected population (Murdoch et al., 2009). Moreover, the microbiological profile of this condition has also changed as a result of the increased prevalence of patients with cardiac devices and prosthetic valves (Wang et al., 2007). Consequently, *S. aureus* has become the leading isolated pathogen associated with IE. In addition, this infecting agent extends beyond the traditional high-risk group and can affect native valves. In the present study, *S. aureus* accounted for 27.4% of all cases of blood culture-positive IE, which is similar to the results observed in previous investigations, which have reported values in the range of 23% to 32% (Murdoch et al., 2009; Chu et al., 2009, 2015; Wang et al., 2007).

The population included in this study shares some features with those from developed countries, including the prevalence of staphylococcal IE, healthcare-associated infections, and comorbidities, which reflects the wide medical advances made throughout the world. On the other hand, the affected patients were younger than in the literature data, with rheumatic valve disease remaining the predominant underlying cardiac condition.

Predictors of in-hospital death

The poor prognosis of IE is mainly related to complications occurring during the in-hospital stay, including embolic events, periannular extension of the infection, and valve dysfunction causing heart failure (Park et al., 2016). These complications are the cause of the high morbidity and mortality during hospitalization.

Previous studies addressing the prognosis of IE have highlighted important predictors of in-hospital mortality (Chu et al., 2004; Wallace et al., 2002). However, many risk factors will only be identified during treatment and not at the time of hospital admission. Heart failure and periannular complications are well-established predictors of an unfavorable outcome, but these are not usually assessed at the diagnosis of IE (Park et al., 2016). Similarly, *S. aureus* infection has been strongly associated with death, but blood cultures pose an inherent delay, and the identification of the infecting microorganism often takes time.

Table 4
Independent variables associated with in-hospital death.

Variables	B coefficient	OR	95% CI	*p*-Value
Age (years)	0.069	1.071	1.019–1.126	0.007
CRP (mg/l)[a]	0.116	1.123	1.039–1.213	0.003
Vegetation length (mm)	0.136	1.146	1.029–1.277	0.003
Embolic events[b]	3.635	12.141	2.051–71.894	0.004
Development of heart failure	1.860	6.425	2.136–19.331	0.001

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.
[a] OR per 10 mg/l of C-reactive protein.
[b] Embolic events after initiation of antibiotic therapy.

The presence of a vegetation by echocardiography is central to the diagnosis of IE. Moreover, vegetation size and mobility have been associated with the risk of systemic embolization, which in turn is a predictor of death. However, the direct impact of vegetation size on mortality has not been well defined. Chu et al. (2004) demonstrated that echocardiographic parameters were useful for diagnosis, but they did not predict the outcome. In contrast, Hill et al. (2008) showed that vegetation length more than 10 mm predicted 6-month mortality, in agreement with the present study.

This study was designed to identify early predictors of in-hospital death in the course of IE. In this regard, CRP at admission could play a major role in predicting the clinical course and outcome of IE. It is one of the most frequently used inflammatory markers that can be obtained routinely in every laboratory. Particularly, in low-income countries, where the delivery of care is limited, a readily available parameter could be of great importance in improving the diagnosis and management of patients with IE.

Most studies assessing CRP in the setting of IE have demonstrated its value in the diagnosis of the disease (Heiro et al., 2005; Olaison et al., 1997). An elevated level of this marker supports the diagnosis of IE, whereas normal levels indicate a low probability of this condition. Indeed, some investigators have suggested the inclusion of CRP as a minor Duke criterion for the diagnosis of IE (Heiro et al., 2005). Although CRP has important value in establishing the diagnosis of IE, data regarding its prognostic implications are scarce. A study including 94 patients with definite IE according to the Duke criteria showed that high serum CRP levels were independently associated with major embolic events during hospitalization (Durante Mangoni et al., 2003). In the present study, CRP levels were associated with death, independent of embolic events.

Other studies have demonstrated the role of serial CRP measurements in predicting the outcome. A study by Verhagen et al., including 123 patients with left-sided native valve IE, showed that the CRP levels after 1 week of treatment and the percentage decline in CRP levels during the first week of treatment were strong predictors of the outcome (Verhagen et al., 2008). However, serious infectious complications including cerebral vascular accident and ischemic cerebral infarction were considered by those authors as poor outcomes, which is different from the present study in which only death was recorded as a poor prognosis. In another study including 129 patients, serial determinations of the CRP levels predicted the outcome, defined as the need for cardiac surgery or death (Heiro et al., 2005). The decrease in serum CRP concentrations was significantly faster in the patients who made an uncomplicated recovery from IE compared with those who required surgery or died. Valve surgery was required in 40% of the cases and 22% of the patients died. In the present study, cardiac surgery was not included as a poor outcome, because surgery can be life-saving in patients with some complications of IE and may not reflect a poor prognosis (Kang et al., 2012). Indeed, a study including 50 patients with IE showed no differences in CRP levels when comparing patients who required surgery with the others (Kocazeybek et al., 2003).

More recently, a prognostic score to predict 6-month mortality was developed for clinical use in IE, based on the combination of four groups of variables: host factors (age, dialysis), IE characteristics (prosthetic or nosocomial IE, causative organism, left-sided valve vegetation), complications (severe heart failure, stroke, paravalvular complication, and persistent bacteremia), and surgical treatment (Park et al., 2016). Similarly, in this study, age was a host factor that remained independently associated with death. Furthermore, IE complications, expressed as embolic events and the development of heart failure, were also predictors of mortality. However, in this investigation, nosocomial IE was not frequent and the IE characteristics that had prognostic value were vegetation size and CRP levels, which also reflects the severity of the infectious process. In addition, although surgery is increasingly performed in complicated IE to improve the outcome, surgical treatment did not affect in-hospital survival in the present study. This may be due to the severity of the condition of patients who underwent a surgical intervention. In the article reporting the score, in which surgery was associated with a lower risk of mortality, this procedure was performed less frequently in the patients at highest risk of death, indicating selection bias for this intervention. On the other hand, in the present study, surgery was performed early during the treatment in the patients with IE complications, in whom the mortality rate without surgery would be higher. Therefore, surgery could have been a factor that protected against a worse outcome in the study patients. Finally, staphylococcal IE was associated with new heart failure and high CRP levels, but did not remain an independent predictor of death after adjustment for surgical treatment.

This study has some limitations. A total of 5% of the patients enrolled met the Duke criteria for possible IE. This may be due to the elevated prevalence of blood culture-negative IE in the study population. Nevertheless, a previous study showed that patients with definite IE by the Duke criteria had an in-hospital mortality rate similar to that of the patients with possible IE (Chu et al., 2004). The reported frequency of IE associated with negative blood culture ranges from 2.5% to 31% (Houpikian and Raoult, 2005), whereas it was 33.5% in the present study, which may be related to the high number of right-sided endocarditis and antibiotic use before blood cultures (Houpikian and Raoult, 2005). Moreover, a heterogeneous population was selected, including patients with right-sided endocarditis who have a better prognosis compared to those with prosthetic valve endocarditis, which is associated with significant mortality and morbidity. However, the patients were recruited prospectively and consecutively from a tertiary center representing a spectrum of disease routinely referred for the management of IE. Despite this wide spectrum of IE presentation, it is not possible to completely rule out the possibility of a predominant inclusion of more severe cases with consequent referral bias and subsequent influence on CRP levels.

Conclusions

In this large cohort of patients with IE, elevated CRP levels at hospital admission and vegetation length at diagnosis were predictors of in-hospital death in patients with IE, independent of other prognostic variables, specifically taking into account the patient characteristics and complications, including the development of heart failure and embolic events.

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Conflict of interest

We declare that we have no conflicts of interest.

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