Incidence, Risk Factors and Subsequent Prognostic Impact of New-Onset Atrial Fibrillation in Infective Endocarditis

Xue-biao Wei, MD; Jie-leng Huang, MD; Yuan-hui Liu, MD, PhD; Chong-yang Duan, MD, PhD; Ze-dazhong Su, MD; Yu Wang, MD; Dan-qing Yu, MD, PhD; Ji-yan Chen, MD, PhD

Background: Few studies with a large sample size have been performed to evaluate the incidence, risk factors and prognostic value of new-onset atrial fibrillation (AF) in patients with infective endocarditis (IE).

Methods and Results: A total of 1,063 IE patients were included and 83 developed new AF. Compared with no-AF, the incidence of in-hospital death (6.0% vs. 22.9%, P<0.001) was higher in patients with new-onset AF. New-onset AF was independently associated with increased risk of in-hospital (adjusted odds ratio [OR]=3.92, P=0.001) and 1-year death (adjusted hazard ratio=2.91, P=0.001), while prior AF was not an independent factor. Kaplan-Meier curve analysis demonstrated new-onset AF mainly affected short-term death (180 days). Age (OR=1.04, P<0.001), rheumatic heart disease (OR=1.88, P=0.022), NYHA Class III or IV (OR=2.09, P=0.003), and left atrial diameter (LAD; OR=1.05, P=0.006) were independent risk factors for development of new AF.

Conclusions: New-onset AF, not prior AF, was a prognostic factor in IE patients, which was mainly associated with increased risk of short-term death. Patients with concomitant rheumatic heart disease, poor cardiac function, and larger LAD had higher risk of developing new AF.

Key Words: Atrial fibrillation; Infective endocarditis; Prognosis

Infective endocarditis (IE) is an uncommon infection of a native or prosthetic heart valve, the endocardial surface, or an indwelling cardiac device. However, the mortality rate is estimated to be 10% at initial hospitalization and increases with long-term follow-up. Therefore, identifying the patients at high risk of death is still urgent.

Atrial fibrillation (AF) is a common arrhythmia in patients with acute conditions attributed to inflammation and hemodynamic change. New-onset AF has a close association with poor outcomes in several conditions, including sepsis, heart failure (HF), and cardiac surgery. Ferrera and co-workers enrolled 507 patients with native left-sided IE, 10.3% of whom developed new AF. They demonstrated that new-onset AF was associated with HF and higher in-hospital mortality. The small sample size and lack of long-term follow-up limited the prognostic evidence of new-onset AF in IE. In addition, factors affecting the development of new AF were not evaluated in previous studies. In order to deal with these uncertainties, the present study with a larger sample size was conducted to assess the prognostic impact of new-onset AF in IE patients, and also to identify its risk factors.

Methods
Study Design
This was a single-center observational study conducted in Guangdong Provincial People's Hospital between January 2009 and July 2015. During the study period, 1,293 patients were diagnosed with IE according to the modified Duke criteria and consecutively enrolled. The exclusion criteria were: age <18 years; readmission record; or diagnosed with IE after major cardiac surgery during the same hospitalization. Finally, 1,063 patients were eligible to be included in this study (Figure 1). The local institutional review board approved the current study and written informed consent was given by all patients after the diagnosis of IE.

Data Collection
After admission, venous blood from at least 3 different sites was collected for blood cultures. We also measured...
C-reactive protein (CRP) and other clinical parameters on the second morning after admission. Transthoracic echocardiography was routinely performed within 24h of admission. Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), and other echocardiographic indices were measured according to the recommendations of the American Society of Echocardiography. Estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease equation for Chinese patients.

Definition of AF
Prior AF was defined as evidence of preexisting AF or atrial flutter (AFL), confirmed by diagnostic code or ECG report before the onset of IE. After being diagnosed with IE, patients underwent continuous 3-lead ECG. In addition, a 12-lead ECG was performed in case of sudden increase in heart rate or loss of regular interval between 2 consecutive R waves. AF or AFL detected in patients without a previous history of AF was considered as new-onset AF. For patients who did not have a previous ECG record and had AF at admission, AF was determined by 2 researchers through the patient’s medical history, symptoms and the results of echocardiography. If AF occurred before IE, it was characterized as previous AF, otherwise new AF.

Follow-up and Endpoints
All patients were followed up for 1 year using telephone-tracking methods. We also reviewed hospital readmission records and outpatient clinic interviews for possible events. The primary endpoint was in-hospital all-cause death, and the secondary endpoint was 1-year death after diagnosis as IE. In addition, the incidences of embolic events and acute HF while in hospital were recorded.

Statistical Analysis
Continuous variables are expressed as mean±SD or median (interquartile range) and differences were compared using variance analysis or non-parametric test. Logarithmic transformation was performed for variables with a skewed distribution. Categorical variables are presented as absolute values and percentages, and differences were compared using the chi-square or Fisher’s exact test. Logistic regression analysis was conducted to determine risk factors for new-onset AF and in-hospital death. The Kaplan-Meier method was used to create survival curves for IE patients according to AF status. Univariable and multivariate Cox proportional hazard analyses were used to test the effects of factors on 1-year mortality. All data were analyzed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). For all analyses, P<0.05 was considered significant.

Results
Baseline Characteristics
During the study period, 1,063 cases of IE (mean age 44±15 years, 70.1% male) were recorded. Among them, 107 had a history of AF and 83 developed new-onset AF. The included patients were divided into 3 groups according to AF status: no-AF (n=873), prior AF (n=107), and new-onset AF (n=83). Baseline characteristics of the studied
Table 1. Baseline Clinical Characteristics

| Clinical variables               | No-AF (n=873) | Prior AF (n=107) | New-onset AF (n=83) | P value |
|---------------------------------|---------------|-----------------|---------------------|---------|
| Demographics                    |               |                 |                     |         |
| Age (years)                     | 42.2±14.8     | 54.8±12.2*      | 52.2±14.8*          | <0.001  |
| Sex, female                     | 255 (29.2)    | 39 (36.4)       | 24 (28.9)           | 0.297   |
| Risk factors                    |               |                 |                     |         |
| Hypertension, n (%)             | 100 (11.5)    | 28 (16.8)       | 19 (22.9)*          | 0.005   |
| Diabetes, n (%)                 | 54 (6.2)      | 13 (12.1)*      | 12 (14.5)*          | 0.003   |
| Smoker, n (%)                   | 145 (16.6)    | 15 (14.0)       | 16 (19.3)           | 0.623   |
| Previous history                |               |                 |                     |         |
| Rheumatic heart disease         | 144 (16.5)    | 67 (62.6)*      | 27 (32.5)*          | <0.001  |
| Congenital heart disease        | 268 (30.7)    | 15 (14.0)*      | 20 (24.1)           | 0.001   |
| Prosthetic valve                | 43 (4.9)      | 30 (28.0)*      | 6 (7.2)             | <0.001  |
| NYHA functional class           |               |                 |                     |         |
| I/II                            | 595 (68.2)    | 55 (51.4)       | 35 (42.2)           | <0.001  |
| III/IV                          | 278 (31.8)    | 52 (48.6)*      | 48 (57.8)*          | <0.001  |
| CRP (mg/L)                      | 21.3 (6.8, 53.9) | 9.4 (2.5, 57.6)* | 22.5 (6.7, 65.3)  | 0.024   |
| eGFR (mL/min/1.73 m²)           | 103.9±42.1    | 85.7±31.2*      | 89.8±41.8*          | <0.001  |
| LV function                     |               |                 |                     |         |
| LAD (mm)                        | 40.5±7.8      | 53.4±9.8*       | 45.0±8.2*           | <0.001  |
| LVEDD (mm)                      | 56.0±10.0     | 55.4±11.9       | 57.8±10.1           | 0.252   |
| LVEF (%)                        | 64.5±8.4      | 62.6±8.8        | 64.9±9.6            | 0.102   |
| Vegetation location, n (%)      |               |                 |                     |         |
| Aortic valve                    | 356 (40.8)    | 42 (39.3)       | 39 (47.0)           | 0.502   |
| Mitral valve                    | 425 (48.7)    | 56 (52.3)       | 38 (45.8)           | 0.656   |
| Aortic and mitral valves        | 64 (7.3)      | 13 (12.1)       | 6 (7.2)             | 0.211   |
| Other                           | 121 (13.9)    | 13 (12.1)       | 5 (6.0)             | 0.123   |
| Culture positive                | 319 (36.5)    | 35 (32.7)       | 30 (36.1)           | 0.739   |
| Surgical treatment              | 619 (70.9)    | 61 (57.0)*      | 61 (73.5)           | 0.009   |

*P<0.05 (compared with no-AF group). AF, atrial fibrillation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 2. Prevalence of adverse events (89 patients did not complete 1-year follow-up). AF, atrial fibrillation.
population are shown in Table 1. Compared with the patients without AF, those with previous or new-onset AF were significantly older and more likely to have a history of diabetes and hypertension. Higher proportions of rheumatic heart disease and prosthetic valves were found in patients with previous AF, in whom the rates of concomitant congenital heart disease and surgical treatment were lower. Cardiac function was worse in patients with previous or new-onset AF, with a higher rate of New York Heart Association (NYHA) functional Class III or IV.

Lower LAD (40.5 ± 7.8 vs. 53.4 ± 9.8 vs. 45.0 ± 8.2, P<0.001) was found in the no-AF group, who had better renal function (eGFR: 103.9 ± 42.1 vs. 85.7 ± 31.2 vs. 89.8 ± 41.8 mL/min/1.73 m², P<0.001).

In-Hospital Events

While in hospital, 87 patients (8.2%) died, 98 (9.2%) suffered acute HF, 117 (11.0%) had embolic events, and 81 (7.6%) suffered from a stroke. Compared with no-AF, the incidence of in-hospital death was higher in patients with new-onset or prior AF (6.0% vs. 15.0% vs. 22.9%, P<0.001, Figure 2). In addition, the incidence of acute HF was significantly higher in new-onset AF compared with no-AF patients (7.3% vs. 26.5%, P<0.05, Figure 2).

The results of univariable logistic regression analysis indicated that the odds ratios (ORs) for in-hospital death were significant for new-onset and prior AF (unadjusted OR 4.69) compared with the no-AF patients (unadjusted OR 2.78). Prior AF was not an independent risk factor for in-hospital death. Compared with no-AF or prior AF, new-onset AF was independently associated with in-hospi-

### Table 2. Adjusted OR and 95% CI for In-Hospital Mortality According to AF Status

| Model       | New-onset AF vs. no-AF | Prior AF vs. no-AF | New-onset AF vs. prior AF |
|-------------|------------------------|--------------------|--------------------------|
|             | OR (95% CI)            | P value            | OR (95% CI)              | P value |
| Unadjusted model | 4.69 (2.62–8.40) | <0.001            | 2.78 (1.52–5.06) | 0.001 |
| Model 1     | 3.44 (1.70–6.95)       | 0.001              | 1.07 (0.51–2.22) | 0.864 |
| Model 2     | 3.66 (1.80–7.43)       | <0.001             | 1.06 (0.50–2.25) | 0.878 |
| Model 3     | 3.55 (1.74–7.22)       | <0.001             | 1.13 (0.53–2.42) | 0.756 |
| Model 4     | 3.66 (1.61–8.29)       | 0.002              | 1.58 (0.64–3.92) | 0.326 |
| Model 5     | 3.92 (1.70–9.04)       | 0.001              | 1.79 (0.69–4.69) | 0.235 |

CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1. Model 1 adjusted for age, diabetes, NYHA Class III/IV, prosthetic valves, eGFR <90 mL/min/1.73 m² and surgical treatment; Model 2 adjusted for Model 1 plus LVEF and mitral valve vegetation; Model 3 adjusted for Model 1 plus aortic valve vegetation and rheumatic heart disease; Model 4 adjusted for Model 1 plus logCRP and LAD; Model 5 adjusted for all significant risk factors including age, diabetes, rheumatic heart disease, NYHA Class III/IV, prosthetic valves, logCRP, eGFR <90 mL/min1.73 m², LAD, LVEF, aortic or mitral valve vegetation and surgical treatment.

### Table 3. Unadjusted and Adjusted HR for 1-Year Mortality

| Clinical variables | Univariable analysis | Multivariable analysis |
|--------------------|----------------------|-----------------------|
|                    | HR       | P value | HR       | 95% CI  | P value |
| Age                | 1.05     | <0.001  | 1.02     | 1.00–1.03 | 0.062 |
| Female sex         | 1.07     | 0.707   | 1.05     | 0.61–1.81 | 0.857 |
| Hypertension       | 1.40     | 0.139   | 1.04     | 0.61–1.79 | 0.881 |
| Diabetes           | 2.58     | <0.001  | 1.51     | 0.86–2.63 | 0.150 |
| Smoker             | 0.95     | 0.825   | 1.04     | 0.61–1.79 | 0.881 |
| Rheumatic heart disease | 1.81 | 0.001   | 1.05     | 0.61–1.81 | 0.857 |
| Congenital heart disease | 0.59 | 0.015   | 1.04     | 0.61–1.79 | 0.881 |
| Prosthetic valve   | 3.87     | <0.001  | 1.65     | 0.92–2.99 | 0.095 |
| NYHA Class III/IV  | 2.77     | <0.001  | 2.57     | 1.69–3.91 | <0.001 |
| LogCRP             | 2.50     | <0.001  | 1.66     | 1.09–2.52 | 0.019 |
| eGFR <90 mL/min1.73 m² | 3.40 | <0.001  | 1.70     | 1.07–2.72 | 0.026 |
| LAD                | 1.03     | <0.001  | 1.01     | 0.98–1.03 | 0.712 |
| LVEDD              | 1.00     | 0.751   | 1.00     | 0.97–1.01 | 0.161 |
| LVEF               | 0.97     | <0.001  | 0.99     | 0.97–1.01 | 0.161 |
| Aortic valve vegetation | 1.68 | 0.003   | 1.70     | 1.05–2.75 | 0.030 |
| Mitral valve vegetation | 0.66 | 0.017   | 1.38     | 0.85–2.23 | 0.189 |
| Culture positive   | 1.04     | 0.819   | 1.01     | 0.98–1.03 | 0.712 |
| Surgical treatment | 0.11     | <0.001  | 0.11     | 0.07–0.27 | <0.001 |

HR, hazard ratio. Other abbreviations as in Tables 1,2.
tal death after adjusting for age, diabetes, NYHA Class III/IV, prosthetic valves, eGFR <90mL/min/1.73 m², and surgical treatment (Table 2, Model 1). Similar results were obtained even after additionally adjusting for LVEF and mitral valve vegetation (Table 2, Model 2), aortic valve vegetation and rheumatic heart disease (Table 2, Model 3) or logCRP and LAD (Table 2, Model 4). In addition, we performed a Model to adjust all significant risk factors including age, diabetes, rheumatic heart disease, NYHA Class III/IV, prosthetic valves, logCRP, eGFR <90mL/min/1.73 m², LAD, LVEF, aortic or mitral valve vegetation and surgery treatment (Table 2, Model 5). The adjusted OR for in-hospital death was 3.92 (95% confidence interval [CI]: 1.70–9.04, P=0.001, Table 2) for new-onset AF compared with no-AF, and no significant difference was found when compared with prior AF (OR=2.19, 95% CI: 0.73, 6.54, P=0.162, Table 2).

### 1-Year Mortality

A total of 974 patients completed the 1-year follow-up and 134 (13.8%) died. Univariable Cox proportional hazard analysis for 1-year death is displayed in Table 3. Compared with the normal group, prior AF (hazard ratio=2.79, P<0.001) and new-onset AF (hazard ratio=3.15, P<0.001) were risk factors for 1-year death. After adjusting for these variables, new-onset AF was independently associated with 1-year death compared with no-AF (hazard ratio=2.91, 95% CI: 1.58–5.38, P=0.001, Table 3). However, prior AF was not an independent risk factor. Kaplan-Meier curve analysis demonstrated significantly worse death in the new-onset AF group compared with prior AF and no-AF (Figure 3).
1-year outcomes in patients with prior or new-onset AF compared with those without AF (log-rank=43.40, P<0.001; Figure 3D). Subgroup analysis showed that new-onset AF mainly affected short-term outcomes (30 days and 30–180 days, Figure 3A–B), but this did not persist after longer follow-up (180–360 days, Figure 3C).

Risk Factors for New-Onset AF
The risk factors for the development of new AF were evaluated by logistic regression analysis in 956 patients (873 no-AF, 83 new-onset AF, Table 4). In the univariable analysis, age, hypertension, diabetes, rheumatic heart disease, NYHA Class III/IV, eGFR <90 mL/min/1.73 m², and LAD were associated with new-onset AF. These variables were included in the multiple logistic regression model, which revealed that age (OR=1.04, 95% CI: 1.02–1.06, P<0.001, Table 4), rheumatic heart disease (OR=1.88, 95% CI: 1.09–3.23, P=0.022, Table 4), NYHA Class III/IV (OR=2.94, 95% CI: 2.09–3.43, P=0.003, Table 4), and LAD (OR=2.09, 95% CI: 1.09–3.23, P=0.022, Table 4) were independent risk factors of new-onset AF.

Discussion
The present study demonstrated that new-onset AF (absence of previous AF) was an independent risk factor for in-hospital death in IE patients. It was associated with increased risk of death in the follow-up period, especially for short-term death (180 days). In addition, older age, concomitant rheumatic heart disease, poor cardiac function, and larger LAD were associated with an increased risk of developing new AF.

A total of 83 (8.7%) IE patients developed new AF in this study. IE is defined as an infection of the endocardium, which may affect 1 or more heart valves, leading to valvular insufficiency and subsequent HF. Hemodynamic deterioration caused by cardiac dysfunction is 1 cause of AF, and other possible mechanisms include the production of excessive catecholamines, activation of the renin-angiotensin-aldosterone system, intracellular calcium overload, increased LV filling pressure and atrial pressure. Besides being a consequence of HF, AF is a cause of HF. In patients exhibiting AF, loss of atrial systole can impair LV filling and decrease cardiac output by up to 25%. In our analysis, the incidence of in-hospital acute HF was significantly higher in patients with new-onset AF compared with those without AF. Previous study also indicated that acute events during a critical illness can accelerate atrial remodeling, which produces a susceptible atrial substrate for developing AF. A larger LAD was found to be associated with increased risk of developing new AF in our study. New-onset AF is proven to be independently associated with unfavorable outcomes in critically ill patients.

Inflammation is another explanation for the development of AF in IE patients. IE is a systemic inflammation caused by infection that is accompanied by an increase in multiple inflammatory cells. Immune cell infiltration into the atria has been reported in several basic studies. Subsequently, inflammatory pathways are activated, which triggers myolysis, cardiomyocyte apoptosis and fibrosis. These changes alter the electrical and structural characteristics of the atrium, resulting in increased vulnerability to AF. The development of AF might reflect excessive inflammation, which appears to be associated with a number of adverse outcomes.

Negative outcomes and new-onset AF shared risk factors, including age and cardiac dysfunction, in our multiple analyses. These variables are established risk factors of poor outcome in IE patients. Taking together all of the evidence presented, new-onset AF could be considered a marker for adverse prognosis in patients with IE. Older age, concomitant rheumatic heart disease, poor cardiac function, and larger LAD are associated with a higher risk of developing new AF, and such patients require more attention.

**Table 4. Univariable and Multivariable Logistic Regression Analyses for New-Onset AF**

| Clinical variables                        | Univariable analysis | Multivariable logistic regression |
|------------------------------------------|----------------------|-----------------------------------|
|                                         | OR                   | P value                           | OR                   | 95% CI    | P value                           |
| Age                                      | 1.05                 | <0.001                            | 1.04                 | 1.02–1.06 | <0.001                            |
| Female sex                               | 0.99                 | 0.955                             |                      |           |                                   |
| Hypertension                             | 2.30                 | 0.003                             | 1.23                 | 0.64–2.35 | 0.533                             |
| Diabetes                                 | 2.56                 | 0.006                             | 1.32                 | 0.62–2.82 | 0.472                             |
| Smoker                                   | 1.20                 | 0.535                             |                      |           |                                   |
| Rheumatic heart disease                  | 2.44                 | <0.001                            | 1.88                 | 1.09–3.23 | 0.022                             |
| Congenital heart disease                 | 0.72                 | 0.212                             |                      |           |                                   |
| Prosthetic valve                         | 1.50                 | 0.366                             |                      |           |                                   |
| NYHA Class III/IV                        | 2.94                 | <0.001                            | 2.09                 | 1.28–3.43 | 0.003                             |
| LgCRP                                    | 1.14                 | 0.542                             |                      |           |                                   |
| eGFR <90 mL/min/1.73 m²                  | 1.87                 | 0.007                             | 0.95                 | 0.57–1.59 | 0.853                             |
| LAD                                       | 1.07                 | <0.001                            | 1.05                 | 1.01–1.08 | 0.006                             |
| LVEDD                                     | 1.02                 | 0.134                             |                      |           |                                   |
| LVEF                                      | 1.01                 | 0.650                             |                      |           |                                   |
| Aortic valve vegetation                  | 1.29                 | 0.273                             |                      |           |                                   |
| Mitral valve vegetation                  | 0.89                 | 0.614                             |                      |           |                                   |
| Culture positive                          | 0.98                 | 0.943                             |                      |           |                                   |
| Surgical treatment                       | 1.16                 | 0.575                             |                      |           |                                   |

Abbreviations as in Tables 1,2.
Another finding in our study was that new-onset AF was associated with a worse prognosis within 180 days after its initiation, but this did not persist after longer follow-up, which concurs with a previous study conducted in critically ill patients. We suspect that new-onset AF is a marker for inflammation and cardiac dysfunction, which portends poor outcomes. However, this did not last for long when this bad state improved.

**Study Limitations**

First, pre-admission silent episodes of AF might have been missed. Second, this was a retrospective analysis based on prospectively collected data. Although multivariable analysis was applied, residual risk factors could have affected the outcomes. Third, the effect of the type or duration of AF was not analyzed because of the small sample size.

**Conclusions**

New-onset AF was an independent risk factor of in-hospital death in IE patients. In addition, it was related to short-term death. New-onset AF could be considered a prognostic value in patients with IE. Greater focus, such as close monitoring, early intervention and strict physiologic management, should be placed on older patients and those with concomitant rheumatic heart disease, poor cardiac function, and larger LAD because of the higher risk of developing new AF.

**Acknowledgments**

None.

**Declaration of Interest**

The authors report no conflicts of interest.

**Funding**

This study was supported by Medical science and Technology Research Funding of Guangdong (grant no. A2019409) and the Fundamental Research Funds for the Central Universities (grant no. 2019MS136). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The work was not funded by any industry sponsors. All authors agreed to submit the manuscript for publication.

**References**

1. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet* 2016; 387: 882 – 893.
2. Toyoda N, Chikwe J, Itagaki S, Geljins AC, Adams DH, Egorova NN. Trends in infective endocarditis in California and New York State, 1998–2013. *JAMA* 2017; 317: 1652 – 1660.
3. Mohkles MM, Ciampichetti I, Head SJ, Talkenberg JJ, Bogers AJ. Survival of surgically treated infective endocarditis: A comparison with the general Dutch population. *Am Thorac Surg* 2011; 91: 1407 – 1412.
4. Fernandez-Hidalgo N, Almirante B, Tornos P, Gonzalez-Alujas MT, Planes AM, Galiñanes M, et al. Immediate and long-term outcome of left-sided infective endocarditis: A 12-year prospective study from a contemporary cohort in a referral hospital. *Clin Microbiol Infect* 2012; 18: E522 – E530.
5. Thuny F, Giorgi R, Habachi R, Assali S, Le Dolley O, Casalta JP, et al. Excess mortality and morbidity in patients surviving infective endocarditis. *Am Heart J* 2012; 164: 94 – 101.
6. Walkey AJ, Benjamin EJ, Lubitz SA. New-onset atrial fibrillation during hospitalization. *J Am Coll Cardiol* 2014; 64: 2432 – 2433.
7. Kaw R, Hernandez AV, Masood I, Gillinov AM, Saliba W, Blackstone EH. Short- and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: A systematic review and meta-analysis. *J Thorac Cardiovasc Surg* 2011; 141: 1305 – 1312.
8. Yamauchi T, Sakata Y, Miura M, Tadaki S, Ushigome R, Sato K, et al. Prognostic impact of new-onset atrial fibrillation in patients with chronic heart failure: A report from the CHART-2 study. *Circ J* 2016; 80: 157 – 167.
9. Kuipers S, Klein KP, Cremer OL. Incidence, risk factors and outcomes of new-onset atrial fibrillation in patients with sepsis: A systematic review. *Crit Care* 2014; 18: 688.
10. Ferrera C, Vilasén I, Fernandez C, López J, Sarriá C, Olmos C, et al. Usefulness of new-onset atrial fibrillation, as a strong predictor of heart failure and death in patients with native left-sided infective endocarditis. *Am J Cardiol* 2016; 117: 427 – 433.
11. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; 30: 633 – 638.
12. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015; 16: 233 – 270.
13. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 2937 – 2944.
14. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A Scientific Statement for healthcare professionals from the American Heart Association. *Circulation* 2015; 132: 1435 – 1486.
15. Dickinson O, Chen LY, Francis GS. Atrial fibrillation and heart failure: Intersecting populations, morbidities, and mortality. *Heart Fail Rev* 2014; 19: 285 – 293.
16. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: What should we do? *Eur Heart J* 2015; 36: 3250 – 3257.
17. Ferreira JP, Santos M. Heart failure and atrial fibrillation: From basic science to clinical practice. *Int J Mol Sci* 2015; 16: 3133 – 3147.
18. Deedwania PC, Lardizabal JA. Atrial fibrillation in heart failure: A comprehensive review. *Am J Med* 2010; 123: 198 – 204.
19. Bosch NA, Cimini J, Walkey AJ. Atrial fibrillation in the ICU. *Chest* 2018; 154: 1424 – 1434.
20. Shaver CM, Chen W, Janz DR, May AK, Darbar D, Bernard R, et al. Atrial fibrillation is an independent predictor of mortality in critically ill patients. *Crit Care Med* 2015; 43: 2104 – 2111.
21. Wetterslev M, Haase N, Hassager C, Belley-Cote EP, McIntyre PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. *Circulation* 2015; 132: 937 – 948.
22. Frustaci A, Chimienti C, Bellucci F, Morgante E, Russo MA, Maseri A. Histologic substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation* 1997; 96: 1180 – 1184.
23. Liao CH, Akazawa H, Tamagawa M, Ito K, Yasuda N, Kudo Y, et al. Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded mouse hearts. *J Clin Invest* 2010; 120: 242 – 253.
24. Friederichs K, Adam M, Remane L, Mollenhauer M, Rudolph V, Rudolph TK, et al. Induction of atrial fibrillation by neutrophils critically depends on CD11b/CD18 integrins. *PLoS One* 2014; 9: e93907.
25. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardioil* 2015; 12: 230 – 243.
26. Heiberg G, Lancellotti P, Antunes MJ, Bougioni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J* 2015; 36: 3075 – 3128.
27. Arrigo M, Ishihara S, Feliot E, Rudiger A, Deye N, Cariou A, et al. New-onset atrial fibrillation in critically ill patients and its association with mortality: A report from the FROG-ICU study. *Int J Cardiol* 2018; 266: 95 – 99.