Abstract: The thickness of epicardial adipose tissue (EAT) was reported to be highly associated with the incidence and severity of atrial fibrillation (AF). This study was conducted to analyze the ability of EAT thickness in predicting adverse cardiovascular (CV) events in AF.

In 190 persistent AF patients, we performed a comprehensive trans-thoracic echocardiographic examination with assessment of EAT thickness. The definition of CV events included CV mortality, hospitalization for heart failure, myocardial infarction, and stroke. There were 69 CV events including 19 CV deaths, 32 hospitalizations for heart failure, 3 myocardial infarctions, and 15 strokes during a mean follow-up of 29 (25th–75th percentile: 17–36) months. The multivariable analysis demonstrates that chronic heart failure, increased left ventricular (LV) mass index and the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, decreased body mass index, and increased EAT thickness (per 1-mm increase, odds ratio 1.224, 95% confidence interval [CI] 1.096–1.368, \( P < 0.001 \)) were associated with adverse CV events. Additionally, the addition of EAT thickness to a model containing CHA2DS2-VASc score, left atrial volume index, and LV systolic and diastolic mitral annulus velocity significantly improved the values in predicting CV events (global \( \chi^2 \) increase 14.65, \( P < 0.001 \) and integrated discrimination improvement 0.10, 95% CI 0.04–0.16, \( P < 0.001 \)).

In AF, EAT thickness was useful in predicting adverse CV events. Additionally, EAT thickness could provide incremental value for CV outcome prediction over traditional clinical and echocardiographic parameters in AF.

Abbreviations: AF = atrial fibrillation, BMI = body mass index, CI = confidence interval, CV = cardiovascular, E = early mitral inflow velocity, E/E' = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, ECG = electrocardiography, eGFR = estimated glomerular filtration rate, IDI = integrated discrimination improvement, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction, LVMI = left ventricular mass index, ROC = receiver-operating characteristic.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the elderly with evidence of an increasing prevalence and incidence worldwide.\(^1\) AF is associated with an increased risk of ischemic stroke, incident myocardial infarction, all-cause mortality, and heart failure.\(^4\)

Epicardial adipose tissue (EAT) represents a real and unique visceral fat deposit of the heart as indicated by the size of its adipocytes, metabolic activity, and biochemical composition. EAT has significantly higher rates of lipolysis and lipogenesis than visceral fat depots of other sites. Because no definite barrier exists between the EAT and the contiguous myocardium, EAT influences the myocardium and adjacent coronary arteries via a paracrine or vasocrine mechanism. Increased EAT thickness is strongly associated with diabetes mellitus, cardiovascular (CV) disease, visceral obesity, subclinical atherosclerosis at multiple locations, and the metabolic syndrome.\(^5\)–\(^9\) EAT is also increased in subjects with AF\(^10\) and is associated with AF severity and the recurrence of AF after catheter ablation.\(^11\) In non-AF patients, increased EAT thickness is shown to be positively associated with the severity of coronary artery disease and left ventricular diastolic dysfunction\(^13\) and is a useful parameter in predicting adverse CV events.\(^14\) However, there was no study to analyze the ability of EAT thickness in prediction of adverse CV events in AF patients. Hence, this study was conducted to evaluate whether EAT thickness was a useful parameter in prediction of adverse CV events in patients with AF. Besides, we also evaluated the major correlates of EAT thickness in these patients.

METHODS

Study Patients

From April 2010 to June 2012, this prospective observational study consecutively enrolled patients diagnosed with persistent AF and referred for transthoracic echocardiography.
The definition of persistent AF was sustained arrhythmia beyond 7 days, which was confirmed by 12-lead electrocardiography (ECG), ECG recording during transfemoral echocardiography, or 24-hour Holter ECG. Our strategy in treating patients with persistent AF was rate control. A total of 225 patients were initially enrolled but those with inadequate echocardiographic visualization ($n = 11$) were excluded first. Then patients with moderate-to-severe valvular heart disease were also excluded ($n = 14$). Ten patients were lost to follow-up. Finally, 190 AF patients were enrolled for further evaluation. The protocol of this study was reviewed and approved by the Institutional Review Board and all enrolled patients signed informed consent forms.

**Echocardiographic Evaluation**

The transthoracic echocardiography was performed using VIVID 7 (General Electric Medical Systems, Horten, Norway) by one independent cardiologist that blind to original patient characteristics according to the standardized protocol, which was also described in our previous studies. The cardiologist was blinded to the clinical data. Patients stayed in the left decubitus position to acquire the anatomic M-mode and 2-dimensional echocardiographic images. The gain was minimized and the wall filter settings were well adapted to eliminate the high-frequency signal. From the apical 4-chamber view, the Doppler sample volume was positioned at the tips of the mitral leaflets to acquire the left ventricular inflow waveforms and at the septal and lateral corners of the mitral annulus to acquire the pulsed tissue Doppler imaging. Early diastolic mitral annulus velocity (E') was averaged from septal and lateral ones. The modified Simpson method, the Devereux-modified method, and the biplane area-length method were used to calculate left ventricular ejection fraction (LVEF), left ventricular mass, and left atrial volume respectively. Left ventricular mass index (LVMI) was defined as left ventricular mass divided by body surface area.

**Characteristics**

| Characteristics | EAT Thickness ≤6.0 mm (n = 97) | EAT thickness >6.0 mm (n = 93) | P       | All patients (n = 190) |
|-----------------|--------------------------------|--------------------------------|---------|----------------------|
| Age, y          | 68 ± 10                        | 73 ± 10                        | <0.001  | 70 ± 10              |
| Male sex (%)    | 67                             | 68                             | 0.914   | 67                   |
| Diabetes mellitus (%) | 26                          | 29                             | 0.614   | 27                   |
| Hypertension (%) | 62                             | 70                             | 0.243   | 66                   |
| CAD (%)         | 5                              | 16                             | 0.014   | 11                   |
| CHF (%)         | 21                             | 37                             | 0.015   | 29                   |
| Stroke (%)      | 15                             | 19                             | 0.479   | 17                   |
| Smoking (%)     | 18                             | 9                              | 0.069   | 13                   |
| SBP, mmHg       | 130 ± 20                       | 135 ± 20                       | 0.093   | 133 ± 20             |
| DBP, mmHg       | 78 ± 12                        | 77 ± 12                        | 0.493   | 77 ± 12              |
| Heart rate, min⁻¹ | 85 ± 21                      | 82 ± 19                        | 0.403   | 83 ± 20              |
| BMI, kg/m²      | 25.6 ± 3.9                     | 26.8 ± 4.3                     | 0.039   | 26.3 ± 4.1          |
| CHA₂DS₂-VASc score | 2.9 ± 1.8                 | 3.9 ± 1.7                      | <0.001  | 3.4 ± 1.8           |
| eGFR            | 56 ± 17                        | 51 ± 17                        | 0.046   | 53 ± 17              |
| Medications     |                                |                                |         |                      |
| Antiplatelet use (%) | 63                          | 55                             | 0.260   | 59                   |
| Anticoagulant use (%) | 24                           | 34                             | 0.104   | 29                   |
| ACEI and/or ARB use (%) | 54                          | 56                             | 0.750   | 54                   |
| β-blocker use (%) | 48                           | 39                             | 0.176   | 44                   |
| CCB use (%)     | 30                             | 39                             | 0.201   | 34                   |
| Diuretics use (%) | 40                           | 44                             | 0.588   | 42                   |
| Echocardiographic data |                  |                                |         |                      |
| LVEDD, mm       | 52 ± 7                         | 52 ± 9                         | 0.754   | 137 ± 40             |
| LVESD, mm       | 36 ± 9                         | 36 ± 10                        | 0.711   | 36 ± 9              |
| LVMI, g/m²      | 54 ± 14                        | 55 ± 15                        | 0.416   | 55 ± 14              |
| LAVI, mL/m²     | 134 ± 44                       | 140 ± 36                       | 0.331   | 137 ± 40             |
| E, cm/s         | 94 ± 20                        | 99 ± 26                        | 0.169   | 96 ± 23              |
| EDT, ms         | 139 ± 29                       | 160 ± 61                       | 0.002   | 149 ± 49             |
| E'/E''          | 9.5 ± 2.3                      | 8.2 ± 2.2                      | <0.001  | 8.9 ± 2.4            |
| EAT thickness, mm | 10.4 ± 3.1                  | 13.0 ± 5.2                     | <0.001  | 11.7 ± 4.5          |

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, DBP = diastolic blood pressure, E = early mitral inflow velocity, E' = early diastolic mitral annulus velocity, E/E' = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, EDT = E-wave deceleration time, eGFR = estimated glomerular filtration rate, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, SBP = systolic blood pressure.
mass divided by body surface area. Left atrial volume index (LAVI) was defined as left atrial volume divided by body surface area.

**Measurement of EAT Thickness**

EAT thickness was measured on the free wall of right ventricle from the parasternal long-axis views by one independent cardiologist. EAT was identified as an echo-free space located between the visceral pericardium and the outer wall of myocardium on the 2-dimensional echocardiography, and EAT thickness was calculated perpendicularly on the free wall of the right ventricle at end-diastole for 3 cardiac cycles.\(^8,22\) The mean value from 3 cardiac cycles was calculated for the later analysis. The aortic annulus was used as anatomical reference of standardized measurement, which was performed at one location on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus. The raw data of echocardiography were stored for off-line analysis using the EchoPAC software (EchoPAC version 08; GE-Vingmed Ultrasound AS GE Medical Systems, Horten, Norway).

Left ventricular dimensions, LVMi, LVEF, and LAVI were measured using the index beat method.\(^{23–25}\) As their measurements were rapid and easy, the early mitral inflow velocity (E), E-wave deceleration time, and E' were averaged from 3 beats. However, a heartbeat was avoided if the duration of a cardiac cycle was too short to finish the diastolic process. Therefore, the measurement of E, E-wave deceleration time, and E' was not consecutive every time.

**Collection of Clinical Data**

Clinical data of AF patients comprising sex, age and history of diabetes mellitus, hypertension, coronary artery disease (CAD), chronic heart failure (CHF), stroke, and smoking were acquired from interviews with patients or medical records. The following definitions were also described in our previous studies.\(^{16,18}\) The readings of systolic and diastolic blood pressures were obtained using a mercury sphygmomanometer. The definition of hypertension was based on a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg or anti-hypertensive drugs prescribed for blood pressure control. The definition of diabetes mellitus was based on antidiabetic agents prescribed to control blood glucose, a fasting blood glucose level >126 mg/dL, or a postprandial blood glucose level >200 mg/dL obtained 2 hours after meals. The definition of body mass index (BMI) was a person’s weight in kilograms divided by the square of height in meters. The definition of stroke was based on a history of cerebrovascular accident including infarction or cerebral bleeding. The definition of CAD was based on any documented coronary angiography, any positive stress test in patients with a history of typical angina, a history of old myocardial infarction, or a history of percutaneous coronary intervention or bypass surgery.

Heart failure was defined according to the Framingham criteria.\(^2\) Myocardial infarction was defined according to the universal definition.\(^23\) Estimated glomerular filtration rate (eGFR) was obtained by using the 4-item Modification of Diet in Renal Disease Study equation.\(^28\)

The prescribed medications comprising antiplatelets, anticoagulants, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, and diuretics were surveyed form the formal medical records in the study period.

**Definition of CV Events**

In AF patients, CV events were defined as CV mortality, myocardial infarction, stroke, and hospitalization for heart failure, which resulted from dyspnea with concurrent intravenous diuretics and with pulmonary congestion confirmed radiographically. The diagnosis of stroke was confirmed by clinical assessment of a neurologist combined with computed tomographic or magnetic resonance imaging findings.

Two cardiologists were selected to determine and judge CV events. If any disagreement was encountered, a third cardiologist was assigned for final judgement after reviewing all clinical data and medical records. If patients had several CV events, only the first event was coded. If patients died after

**TABLE 2. Univariable and Multivariable Correlates of EAT Thickness in Study Patients**

|                      | Univariable Analysis | Multivariable Analysis |
|----------------------|----------------------|------------------------|
|                      | r        | P        | β         | P        |
| Age, y               | 0.367    | <0.001   | 0.343     | <0.001   |
| Male sex             | −0.037   | 0.617    |           |          |
| Diabetes mellitus    | 0.077    | 0.289    |           |          |
| Hypertension         | 0.062    | 0.398    |           |          |
| CAD                  | 0.174    | 0.016    |           |          |
| CHF                  | 0.122    | 0.095    |           |          |
| Stroke               | 0.061    | 0.405    |           |          |
| Smoking              | 0.134    | 0.065    |           |          |
| SBP, mmHg            | 0.133    | 0.091    |           |          |
| DBP, mmHg            | −0.078   | 0.340    |           |          |
| Heart rate, min⁻¹    | 0.013    | 0.862    |           |          |
| BMI, kg/m²           | 0.128    | 0.086    |           |          |
| CHA₂DS₂-VASc score   | 0.304    | <0.001   | −0.184    | 0.013    |
| eGFR                 | −0.026   | 0.719    |           |          |
| Medications          |          |          |           |          |
| Antiplatelet use (%) | −0.119   | 0.101    |           |          |
| Anticoagulant use (%)| 0.047    | 0.520    |           |          |
| ACEI and/or ARB use (%)| 0.057   | 0.436    |           |          |
| β-Blocker use (%)    | 0.173    | 0.017    | 0.161     | 0.020    |
| CCB use (%)          | 0.005    | 0.945    |           |          |
| Diuretics use (%)    | 0.026    | 0.763    |           |          |
| Echocardiographic data|          |          |           |          |
| LVEDD, mm            | 0.045    | 0.534    |           |          |
| LVEDD, mm            | 0.045    | 0.534    |           |          |
| LVEF (%)             | −0.039   | 0.594    |           |          |
| LVMi, g/m²           | 0.161    | 0.031    |           |          |
| LAVI, mL/m²          | −0.024   | 0.745    |           |          |
| E', cm/s             | 0.064    | 0.382    |           |          |
| EDT, ms              | 0.157    | 0.031    |           |          |
| E/E'                 | −0.276   | <0.001   | 0.263     | <0.001   |
| ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, DBP = diastolic blood pressure, E = early mitral inflow velocity, E' = early diastolic mitral annulus velocity, E/E' = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EDT = e wave deceleration time, eGFR = estimated glomerular filtration rate, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-systolic dimension, LVMi = left ventricular mass index, SBP = systolic blood pressure.
episodes of heart failure, myocardial infarction, or stroke during the same admission, they were coded as CV deaths. In patients reaching the study end points, they were followed until the first episode of adverse events, whereas the other patients received follow-up until March 2014.

Reproducibility

To investigate the interobserver variability of measurement of EAT thickness, 30 patients were randomly chosen by 2 independent observers. Then identical measurement of echocardiographic parameters was repeated 1 week later to investigate the intraobserver variability. The mean percent error was obtained by dividing the absolute difference by an average of above 2 observations.

Statistical Analysis of Clinical Data

We used the SPSS 18.0 software (SPSS Inc, Chicago, IL) for further statistical analysis. Clinical data were listed as mean ± standard deviation, percentage, or median values (25th–75th percentile) for the follow-up period. We compared categorical and continuous variables between 2 groups by using the χ² test and independent samples t test, respectively, and investigated any relationship between 2 continuous variables by using the bivariate correlation method. Significant variables in the univariable analysis were chosen for further multivariable analysis. Cox proportional hazards model with forward selection was used to identify the predictors of adverse CV events. To define the best cut-off of EAT thickness, we calculated the Youden index (sensitivity + specificity / 2) by using the receiver-operating characteristic curve.

| TABLE 3. Predictors of Cardiovascular Events Using Cox Proportional Hazards Model |
|-------------------------------------|-----------------|-----------------|
|                                     | Univariate      | Multivariate (Forward) |
|                                      | HR (95% CI)     | P               | HR (95% CI)     | P               |
| Age, y                               | 1.048 (1.022–1.075) | <0.001          | 2.508 (1.455–4.323) | 0.001          |
| Male sex                             | 0.831 (0.494–1.398) | 0.485          | 0.975 (0.574–1.654) | 0.924          |
| Diabetes mellitus                    | 1.190 (0.706–2.005) | 0.513          | 1.126 (0.698–1.817) | 0.626          |
| Hypertension                         | 0.788 (0.486–1.278) | 0.335          | 1.015 (0.631–1.632) | 0.950          |
| CAD                                  | 0.910 (1.002–3.642) | 0.049          | 1.125 (0.685–1.850) | 0.642          |
| CHF                                  | 3.025 (1.883–4.858) | <0.001         | 0.971 (0.956–0.987) | <0.001         |
| Stroke                               | 0.969 (0.508–1.848) | 0.923          | 0.974 (0.959–0.990) | 0.001          |
| Smoking                              | 0.357 (0.130–0.981) | 0.046          | 0.900 (0.841–0.962) | 0.002          |
| SBP, mmHg                            | 1.004 (0.991–1.018) | 0.531          | 1.271 (1.118–1.446) | <0.001         |
| DBP, mmHg                            | 1.005 (0.983–1.027) | 0.661          | 0.097 (0.956–0.987) | <0.001         |
| Heart rate, min⁻¹                    | 1.002 (0.990–1.014) | 0.748          | 1.105 (1.059–1.143) | <0.001         |
| BMI, kg/m²                            | 0.900 (0.841–0.962) | 0.002          | 0.971 (0.956–0.987) | <0.001         |
| CHA2DS2-VASc score                   | 1.271 (1.118–1.446) | <0.001         | 0.974 (0.959–0.990) | 0.001          |
| eGFR                                 | 0.971 (0.956–0.987) | 0.001          | 0.974 (0.959–0.990) | 0.001          |
| Medications                          |                  |                |                  |
| Antiplatelet use (%)                 | 1.064 (0.656–1.726) | 0.803          | 0.975 (0.574–1.654) | 0.924          |
| Anticoagulant use (%)                | 0.975 (0.574–1.654) | 0.924          | 1.126 (0.698–1.817) | 0.626          |
| ACEI and/or ARB use (%)              | 1.126 (0.698–1.817) | 0.626          | 1.015 (0.631–1.632) | 0.950          |
| β-Blocker use (%)                    | 1.015 (0.631–1.632) | 0.950          | 1.125 (0.685–1.850) | 0.642          |
| CCB use (%)                          | 1.125 (0.685–1.850) | 0.642          | 1.902 (1.184–3.058) | 0.008          |
| Diuretics use (%)                    | 1.902 (1.184–3.058) | 0.008          |                  |                |
| Echocardiographic data               |                  |                |                  |
| LVEDD, mm                            | 1.031 (0.999–1.064) | 0.056          | 1.031 (0.999–1.064) | 0.056          |
| LVESD, mm                            | 1.039 (1.013–1.067) | 0.004          | 1.039 (1.013–1.067) | 0.004          |
| LVMI, g/m²                            | 0.968 (0.953–0.984) | <0.001         | 0.968 (0.953–0.984) | <0.001         |
| LAVI, mL/m²                           | 1.013 (1.007–1.019) | <0.001         | 1.013 (1.007–1.019) | <0.001         |
| LAVI, mL/m²                           | 1.012 (0.999–1.024) | 0.065          | 1.012 (0.999–1.024) | 0.065          |
| E, cm/s                               | 1.008 (0.998–1.018) | 0.117          | 1.008 (0.998–1.018) | 0.117          |
| EDT, ms                               | 1.004 (1.000–1.009) | 0.066          | 1.004 (1.000–1.009) | 0.066          |
| E’, cm/s                              | 0.771 (0.690–0.862) | <0.001         | 0.771 (0.690–0.862) | <0.001         |
| E/E’                                  | 1.100 (1.059–1.143) | <0.001         | 1.100 (1.059–1.143) | <0.001         |
| EAT thickness, mm                     | 1.286 (1.168–1.417) | <0.001         | 1.286 (1.168–1.417) | <0.001         |

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, BMI = body mass index, CAD = coronary artery disease, CCB = calcium channel blocker, CHF = chronic heart failure, CI = confidence interval, DBP = diastolic blood pressure, E = early diastolic mitral annulus velocity, E/E’ = the ratio of transmitral E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, EDT = E wave deceleration time, eGFR = estimated glomerular filtration rate, HR = hazard ratio, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic dimension, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic dimension, LVMI = left ventricular mass index, SBP = systolic blood pressure. Covariates in this multivariate model included the significant variables in univariable analysis (age, smoking, CAD, CHF, BMI, CHA2DS2-VASc score, eGFR, diuretic use, LVESD, LVMI, LVEF, E’, E/E’, and EAT thickness).
characteristic (ROC) curve. We also evaluated incremental model performance by calculating sequential change of the \( \chi^2 \) value and performed the Kaplan–Meier survival analysis of CV events. Besides, we performed stepwise multiple linear regression analysis to identify the correlates of EAT thickness. Finally, incremental model performance was also assessed by Integrated Discrimination Improvement (IDI) using SAS 9.3 (SAS Institute, Cary, NC). Statistical significance was recognized if \( P < 0.05 \) in 2-sided tests.

**RESULTS**

Our final study population included 190 persistent AF patients (128 male and 62 female) with a mean age of 70 ± 10 years. In ROC curve analysis, we found that 6.0 mm was the best cutoff value of EAT thickness in the prediction of CV events. Table 1 demonstrates the comparison of traditional clinical and echocardiographic characteristics according to EAT thickness. We found that age, the prevalence of CAD, CHF, BMI, CHA2DS2-VASc score, LAVI, LVEF, E/E', and EAT thickness were associated with adverse CV events in the univariable analysis. After performing the multivariable analysis, the existence of CHF, lower BMI and eGFR, and higher LVMI and EAT thickness were still independent predictors of adverse CV events in AF patients.

**TABLE 4. Incremental Values of EAT Thickness in Relation to CV Events**

| CV Events | Incremental Values | \( P \) | IDI | \( P \) |
|-----------|--------------------|------|-----|-----|
| Model 1: CHA2DS2-VASc score | Reference | | | |
| Model 2: model 1 + LAVI, LVEF, E/E' | 28.21 | \(<0.001\) | Reference | |
| Model 3: model 2 + EAT thickness | 14.65 | \(<0.001\) | 0.10 | \(<0.001\) |

\( P \) value based on the difference in \( \chi^2 \) value was compared with the previous model. \( P \) value based on IDI was compared with the model 2. CV = cardiovascular, E/E' = the ratio of transmural E-wave velocity to early diastolic mitral annulus velocity, EAT = epicardial adipose tissue, IDI = integrated discrimination improvement, LAVI = left atrial volume index, LVEF = left ventricular ejection fraction.

were significantly different between patients with EAT thickness \( \leq 6.0 \text{mm and} >6.0 \text{mm}. \)

Table 2 demonstrates univariable and multivariable correlates of EAT thickness in AF patients. We found that older age, the existence of CAD, higher CHA2DS2-VASc score, lower eGFR, the prescription of calcium channel blockers, higher LVMI, longer E-wave deceleration time, lower E', and higher E/E' were correlated with higher EAT thickness in the univariable analysis. After performing the multivariable analysis, older age, the prescription of calcium channel blockers, and higher E/E' were still correlated with higher EAT thickness.

The follow-up duration of AF patients experiencing CV events was 29 (25th–75th percentile: 17–36) months. Sixty-nine CV events, including CV death (n = 19), hospitalization for heart failure (n = 32), myocardial infarction (n = 3), and stroke (n = 15) were recognized during the follow-up period. The total amount of person-years was 459 and incidence rate of CV events was 15.0% per year during follow-up. Table 3 shows predictors of CV events using the Cox proportional hazards regression analysis. We found that older age, the existence of CAD and CHF, non-smoking status, lower BMI, higher CHA2DS2-VASc score, lower eGFR, diuretic use, larger left ventricular end-systolic dimension, lower LVEF, higher LVMI, lower E', higher E/E', and higher EAT thickness were associated with adverse CV events in the univariable analysis. After performing the multivariable analysis, the existence of CHF, lower BMI and eGFR, and higher LVMI and EAT thickness (hazard ratio, 1.211; 95% confidence interval [CI], 1.084–1.351; \( P < 0.001 \)) were still independent predictors of adverse CV events in AF patients.

Figure 1 demonstrates the Kaplan–Meier curves for CV event-free survival in study patients subdivided according to EAT thickness (log-rank \( P < 0.001 \)) and showed a trend in further identifying CV events in females with a CHA2DS2-VASc score of 0 (IDI 0.13, 95% CI 0.05–0.21, \( P = 0.002 \)) and showed a trend in further identifying CV events in females with a CHA2DS2-VASc score of 1 (IDI 0.10, 95% CI 0.01–0.20, \( P = 0.056 \)), when compared with a Cox model containing CHA2DS2-VASc score, LAVI, LVEF, and E/E'.

For measurement of EAT thickness, our result demonstrated that the intraobserver mean percent error was
7.1% ± 10.1%, whereas the interobserver mean percent error was 8.3% ± 12.1%.

**DISCUSSION**

Our study estimated the association of EAT thickness with adverse CV events in patients with documented AF. We found that higher EAT thickness was associated independently with further risks of adverse CV events in AF patients. Additionally, the EAT thickness could add significant incremental values beyond the conventional clinical and echocardiographic parameters in prediction of adverse CV events.

EAT represents a type of visceral adipose tissue adjacent the heart and has a unique character in terms of the biochemical composition, the size of its adipocytes, and metabolic activity. EAT has been proposed to influence the development of coronary atherosclerosis owing to its endocrine and paracrine activity by secreting anti-inflammatory and proinflammatory cytokines and chemokines. Several studies showed age and BMI were associated significantly with EAT thickness. In patients diagnosed with metabolic syndrome, Park et al. found that E/E' was associated significantly with EAT thickness. Several studies showed that higher EAT thickness was associated independently with left ventricular diastolic dysfunction. Left ventricular diastolic dysfunction was correlated to poor CV prognosis.

In the general population, Mahabadi et al. found an association between EAT and incident myocardial infarction and CV risk factors. In the cross-section study by Akil et al., the EAT thickness in patients diagnosed with ischemic stroke was found to be higher than those in healthy controls. Several studies have shown EAT thickness is associated significantly with left ventricular diastolic dysfunction. Left ventricular diastolic dysfunction was correlated to poor CV prognosis.

In our study, the multivariable analysis consistently revealed that increased E/E' and old age were independently associated with increased EAT thickness. Old age is a well-recognized risk factor of adverse CV events. E/E' was also a strong predictor of adverse CV events in various population including patients with type 2 diabetes mellitus, chronic kidney disease, and dialysis. Our present results found EAT thickness as a useful predictor for adverse CV events even after adjustment for many important clinical and echocardiographic parameters.
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