**E/e’ Ratio Is a Strong Prognostic Predictor of Mortality in Patients With Non-Valvular Atrial Fibrillation With Preserved Left Ventricular Systolic Function**

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**Background:** The purpose of this study was to investigate the prognostic values of the E/e’ ratio and other echocardiographic and clinical parameters in patients with non-valvular atrial fibrillation (AF) with preserved left ventricular (LV) systolic function.

**Methods and Results:** A total of 488 patients (322 men, age: 66±11 years) with non-valvular AF with preserved LV systolic function (LV ejection fraction >50%) were included. The E and e’ velocities were measured in 5 consecutive heart beats and averaged. Mean follow-up duration after enrollment was 17.7±5.3 months. All-cause deaths occurred in 45 patients (cardiovascular deaths: n=29). There were significant differences in age (65.6±11.3 vs. 71.5±9.1, P<0.001) and hemoglobin concentration (13.6±2.9 vs. 11.5±3.4 g/dl, P<0.0001) between the deceased group and the survivors. E/e’ ratio in the deceased group was significantly higher than that in the survivors (17.67±3.39 vs. 10.8±3.30, P<0.001). Survival analysis showed that a high E/e’ ratio (>15.0) represents a poorer prognosis (P<0.001 by Log-Rank test) than an E/e’ ratio of 15 and below. Multivariate analysis identified 2 significant variables that were predictive of all-cause deaths: hemoglobin (hazard ratio (HR)=0.806, 95% confidence interval (CI)=0.733–0.886, P<0.0001), and E/e’ >15 (HR=3.064, 95%CI=1.38–6.804, P=0.006).

**Conclusions:** E/e’ ratio is a useful independent prognostic parameter for predicting mortality in patients with AF with preserved LV systolic function.  

**Key Words:** Atrial fibrillation; Echocardiography; Prognosis
Study Population
The study population consisted of 488 consecutive patients (322 men; age: 66±11 years) with non-valvular AF with normal left ventricular systolic function (LVEF >50%) who were screened from 2006 to 2008 at Samsung Medical Center, Seoul, Korea. Non-valvular AF was defined as AF without significant (moderate or greater) valvular heart disease. Exclusion criteria were: presence of heart failure, congenital heart disease, cardiomyopathy, permanent pacemakers, paroxysmal AF, uncontrolled tachycardia or bradycardia, and uncontrolled pulmonary disease or thyroid dysfunction. Clinical data including past medical history, presence of risk factors, and medications were obtained by complete review of each patient’s medical record and laboratory findings. A CHADS2 score ranging from 0 to 6 was calculated for each patient as: congestive heart failure (CHF) (1 point); hypertension (1 point); age >75 years (1 point); diabetes (1 point); and history of stroke, transient ischemic attack, or systemic embolism (2 points). The study was approved by the institutional ethical review board.

Conventional Echocardiographic Evaluation
Comprehensive transthoracic echocardiography was performed using commercially available equipments (Vivid 7, GE Medical system, Milwaukee, WI or Acuson 512, Siemens Medical Solutions, Mountain View, CA or Sonos 5500, Philips Medical System, Andover, MA, USA). Standard M-mode, 2-dimensional, and color Doppler imaging were performed in parasternal and apical views with patients in the left lateral decubitus position. End-diastole was defined as the frame with the largest cavity area immediately before the onset of the QRS and end-systole as the frame with the smallest cavity area. LV end-diastolic volume, LV end-systolic volume, and LVEF were calculated from 2-dimensional recordings using the modified biplane Simpson’s method.

Relative wall thickness (RWT) was calculated as follows: RWT = [(posterior wall thickness + interventricular septal wall thickness)/LV end-diastolic dimension]. LV mass was calculated as reported previously and indexed to body surface area (LVMi). Left atrial (LA) volume was assessed by the modified biplane area-length method and was indexed to body surface area (LAVI).
Doppler Flow and Tissue Doppler Imaging Measurements
Early diastolic mitral inflow velocity (E) was measured using the pulsed wave Doppler method, by placing the sample volume at the level of the mitral valve leaflet tips. The tissue Doppler-derived early diastolic mitral annular velocity (e’) was measured from the septal corner of the mitral annulus in the apical 4-chamber view. Deceleration time of early transmitial flow velocity (DT) was also measured. The average of 5 consecutive Doppler signals was used.

Measurement of Biomarkers
Plasma was immediately separated from the blood element by centrifugation at 4°C for the measurement of NT-pro brain natriuretic peptide (BNP) using enzyme-linked immunosorbent assay according to the manufacturer’s instructions (Biomedica, Wien, Austria). The minimum detectable quantity of human NT-pro BNP was 5 pmol/ml. The intra-assay and inter-assay coefficients of variation for all enzyme immunoassays were <5% and <10% respectively. C-reactive protein concentrations were normalized by logarithmic transformation before they were analyzed. Since the standard error of the mean of NT-proBNP levels was too wide, the Mann–Whitney non-parametric U test was used in the analysis between the survivors and deceased group.

Interobserver and intraobserver variability for mean measurement of early diastolic mitral inflow velocity (E) and tissue Doppler-derived early diastolic mitral annular velocity (e’) during 5 cardiac cycles was determined from the analysis of the Doppler-echocardiographic images of 10 randomly selected patients by 2 independent observers. The results were compared with a one-way ANOVA, Pearson correlation coefficient, and Bland–Altman method.

Logistic regression analysis was performed to identify independent predictors of death. Cumulative survival curves during follow up of patients with lower vs. higher E/e’ were obtained by the Kaplan–Meier method with a log rank test. The E/e’ ratio of 15 was selected by the minimum P-value approach by Log-Rank test. Univariate and multivariate cox proportional hazard regression model was carried out for all-cause deaths. Variables for univariate analysis included sex, age, body surface area, LVEF, LAVI, LVMi, E’, e’, DT, logNT-proBNP, high-sensitivity C-reactive protein (hsCRP), hemoglobin, E/e’, E/e’>15, history of hypertension, diabetes, hypercholesterolemia, CHF, stroke, and ischemic heart disease (IHD). For multivariate analysis, significant P-value variables in univariate analysis and other important clinical variables irrespective of their univariate P-value were included into the model. P-values <0.05 were considered to be statistically significant.

SPSS 15.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Results
Clinical and Echocardiographic Characteristics of the Subjects
The mean age of the patients was 65.9±11.2 and 66% of them were male. Mean follow-up duration after enrollment was 17.7±5.3 months. Of the 488 patients, all-cause death occurred in 45 patients and cardiovascular death occurred in 29 patients. There were no significant differences in gender, history of hypertension, diabetes, hypercholesterolemia, CHF, stroke, IHD, CHADS2 score, or medications between the deceased group and the survivors. There were significant differences between the deceased group and the survivors regarding age, log NT-proBNP, hsCRP, and hemoglobin (Table 1).

There were no significant differences in interventricular septum thickness, posterior wall thickness, LVIDd, LVIDs, LV mass, and LVEF between the deceased group and the survivors. LA volume and LAVI were similar between the 2 groups. There were significant differences between the deceased group compared to the survivors (Table 2). Intraobserver variability of E/e’ measurement was 3.9±7.2%, and interobserver variability was 4.3±8.4%, respectively.

The E/e’ Ratio and All-Cause Deaths
To evaluate the effect of LV diastolic function or LV filling pressure on outcome, E/e’ ratio was stratified according to all-cause deaths and cardiac deaths (group A: E/e’ ≤15, group B: E/e’>15). Of the 488 patients, 61 patients were in group B. Compared with group A, group B consisted of significantly
older (P<0.0001) subjects, more women (P<0.0001), had a lower body surface area (P=0.006), and were more likely to have hypertension (P=0.006), history of CHF (P=0.019), and history of coronary artery bypass grafts (P=0.028). Cardiovascular deaths and all-cause deaths were significantly increased in group B compared with group A.

NT-pro BNP concentrations were available for 255 of the 427 (59.7%) patients in group A and 48 of the 61 (78.7%) patients in group B. The hsCRP concentrations were available for 291 of the 427 (68.1%) patients in group A and 50 of the 61 (82%) patients in the group B. Hemoglobin concentration was available in all patients in both groups. Patients in group B had higher levels of log NT-pro BNP (P=0.003) and lower hemoglobin concentration (P<0.0001) (Table 3).

There were no significant differences in interventricular septum thickness, posterior wall thickness, LVIDd, LVIDs, RWT, and LVEF between the 2 groups. LA, LAVI, and LVMI were significantly increased in group B compared with group A (P<0.001, P=0.001, and P=0.001). E velocity (P<0.001), DT (P=0.001), and E/e' (P<0.0001) were significantly greater in group B. e' velocity was significantly smaller in group B (P<0.0001) (Table 4).

Kaplan–Meier analysis showed that the survival rate during follow up was significantly higher in group A than in group B (log rank P<0.001) (Figure). Multivariate Cox-regression analysis identified 2 significant independent variables that were predictive of all-cause of deaths: hemoglobin concentration (hazard ratio (HR)=0.806, 95% confidence interval (CI)=0.733–0.886, P<0.0001), and E/e'>15 (HR =3.064, 95%CI =1.38–6.804, P=0.006) (Table 5). To investigate the possible impact of DT on outcome, patients were divided into 2 groups according to DT>140 ms (n=409 (83.8%)) and DT≤140 ms (n=65 (13.3%)). DT was not a prognostic predictor in Cox-regression analysis.

### Discussion

The principal finding of this study was that the E/e' ratio, an estimate of LV filling pressure, was a useful predictor of clinical outcome in patients with non-valvular AF with preserved
LV systolic function, and a cut-off value of E/e’ ratio 15 proved to be superior to other clinical or echocardiographic parameters as a prognostic indicator.

The incidence of AF increases with age, and among the population of over 65 years of age, about 10% have AF. Non-valvular AF is an important clinical condition not only because of its strong relationship with ischemic stroke but also due to subsequent cardiac mortality and morbidity.

A number of previous studies have reported the prognostic factors on mortality in patients with non-valvular AF with various degrees of LV systolic dysfunction, and they were: diabetes, increased age, heart failure, myocardial infarc-
tion or IHD, systolic dysfunction on echocardiography, smoking, and cerebrovascular disease. Among these multiple factors, LV systolic dysfunction was the most common significant prognostic factor in non-valvular AF. However, prognostic indicators in non-valvular AF with preserved LV systolic function have not been clarified.

The ratio of early transmitral flow velocity (E) to early diastolic septal mitral annular velocity (‘e’) has been shown to be the most accurate non-invasive method of estimation of elevated LV filling pressure. Increased value of E/e’ ratio indicates a raised LV filling pressure in both normal sinus rhythm and AF, and the E/e’ ratio has been reported to be valuable for prediction of prognosis in patients in a variety of cardiac diseases. E/e’ ratio has also been validated for LV diastolic filling pressure assessment in chronic AF.

A recent study by Okura et al in 230 subjects revealed the E/e’ ratio as a predictor of clinical outcome in patients with non-valvular AF. Cumulative survival rate was significantly lower in the group whose E/e’ was greater than 15 than in the group with E/e’ ≤15. Considering this study, E/e’ >15 seems a suitable index for predicting elevated LV end-diastolic pressure (LVEDP) in non-valvular AF. In our present study, we showed that an increased E/e’ of over 15 is associated with risk of death in patients with non-valvular AF whose LV systolic function is preserved. To our knowledge, this is the first large-scale study showing that the E/e’ ratio is the strongest independent echocardiographic prognostic predictor in this group of patients. The study by Okura et al did include a proportion of subjects with preserved LV systolic function, and although our study showed similar results, our results differ significantly from the previous study in terms of patient characteristics. The population of the previous study was heterogeneous with an admixture of subjects with decreased and preserved ejection fraction, whereas our subjects were limited to patients with preserved LV systolic function. Furthermore, although the study separately analyzed subjects with normal LV systolic function, the number of the subjects was relatively small. By exclusively enrolling a large number of subjects with normal LV systolic function among the patients with non-valvular AF, we could clarify the importance of E/e’ as a predictor of clinical outcome in this group. Another important issue that separates our study from the previous one is the independence of the E/e’ ratio as a risk factor regardless of age. According to our results, only the E/e’ ratio and hemoglobin concentration were independent prognostic factors for mortality in patients with non-valvular AF with normal systolic function, whereas in the previous study, age was also an independent predictor. In the previous study, the mean age of the enrolled patients were relatively high (72±11 years), and clearly a number of significantly old subjects at diagnosis were included. This might have resulted in signifying age as a main factor on mortality. Our subjects were younger (mean age 66±11 years), and consequently we might have been able to eliminate the age factor and elucidate the importance of the E/e’ ratio regardless of age. Regarding the hemoglobin concentration as a prognostic indicator, our study is in correspondence with a previous study that demonstrated anemia as an independent predictor of mortality and hospitalization in elderly patients with AF.

DT, which has been known as a strong predictor of mortality in patients with systolic dysfunction, was not a significant predictor of mortality in our study population, which consisted of patients with non-valvular AF with preserved LV systolic function. Previous studies have shown that DT ≤140 ms is a significant indicator of poor prognosis in patients with various cardiac diseases and also in AF, but the results were mainly limited to subjects with decreased LV systolic function. Our study was performed to evaluate the echocardiographic and clinical prognostic factors in patients with AF whose systolic LV function is preserved, especially regarding the degree of LV filling pressure. DT was not a prognostic predictor in our study. This might be the main explanation for the discrepancy between the previous results and our results. Additionally, as our study subjects were restricted to patients with normal LV systolic function, only 65 (13.3%) patients presented with DT≤140 ms. It might be possible to conclude that DT can serve as a predictor of mortality in patients with AF only when LV systolic function is decreased. There might be several reasons of this finding, which are: DT reflects not only LV filling pressure but also myocardial relaxation, and the extent of change in relaxation is quite variable in patients with preserved systolic function. This random fluctuation might have obscured any significance that the DT could have against prognosis in patients with preserved LV systolic function. This is supported by the fact that the DT is not a significant predictor of outcome in patients with hypertrophic cardiomyopathy. Furthermore, as the value of DT similar in subjects with grade 2 diastolic dysfunction (ie, ‘pseudonormal’ mitral inflow pattern) and normal LV diastolic function, making it difficult to discriminate these 2 states by itself, DT might not be a suitable measure of diastolic dysfunction in subjects with AF and preserved systolic function.

Another interesting fact in our study is the subject of LA volume. LAVI is associated with diastolic dysfunction and is related to cardiovascular risk in various conditions and is a predictor of outcome in patients with CHF and in sinus rhythm. However, in our study, there was no significant difference in LAVI between the deceased group and the survivors. In AF, the subject of LA enlargement should be interpreted with more caution. Tachycardia-induced atrial myopathy leads to advanced remodeling of the atrium with fibrosis independent of increased LV filling pressure, and consequently, LAVI might not be a suitable surrogate of diastolic dysfunction in subjects with AF. Our results support this finding, and we conclude that LAVI might not be useful as a predictor of clinical outcome in AF, especially in cases with preserved LV systolic function.

Study Limitations
There are several limitations in this study. First, measurements of E and e’ were not performed simultaneously. Beat-to-beat variation of the indices might affect the result of E/e’ calculation in patients with AF. Following the methods from previous reports and recommendations by the American Society of Echocardiography (ASE), we used the average value of measurements from 5 consecutive beats for all Doppler analysis. Second, this was a single-center retrospective study. These results therefore need to be confirmed by a larger, prospective, multicenter study. Third, this study did not include the effect of drugs or hemodynamic alteration on E/e’. These parameters might have affected the prognosis of the patients. Fourth, NT-proBNP and hsCRP were not available in all of the patients. NT-proBNP was available in 255 patients (62.1%) and hsCRP was available in 341 patients (69.9%). This might have resulted in underestimation of the value of these indices as prognostic indicators, and this fact could need further elucidation.

Conclusion
Our data suggest that E/e’, reflecting LV diastolic dysfunction
and LV filling pressure, and anemia are strong predictors of all-cause mortality in patients with non-valvular AF with preserved LV systolic function.

References