Left ventricular diastolic dysfunction: a new foe in the management of atrial fibrillation?

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and in public health, and its prevalence and incidence is increasing globally. In total, 33.5 million individuals, or 0.5% of the world's population have AF, and this "global epidemic" have a profound impact not only on individual disability and mortality but also on the global health care economy. The recent analysis of Global Burden of Disease (GBD) database revealed that a small increase in AF prevalence and a significant increase in the overall incidence of AF from 1990 to 2010 (1). The estimated AF prevalence rate per 100 000 individuals was 569.5 in males and 359.9 in females in 1990, and it increased to 596.2 in males and 373.1 in females in 2010. The overall incidence of AF per 100 000 individuals was 60.7 in males and 43.8 in females in 1990, and it increased to 77.5 in males and 59.5 in females by 2010 (1). In the United States of America, it is estimated that 2.66 million people will have AF in 2010, and that the number will increase to 12 million by 2050 (2).

The age-adjusted mortality rate for AF also increased twofold in men and women and it increased steadily through 1995, 2000, and 2005, especially in the developed world. By 2010, the age-adjusted mortality rate per 100 000 individuals was 1.6 and 1.7 for men and women, respectively. Disability associated with AF also increased significantly from 1990 to 2010. An 18% increase in disability-adjusted life-years per 100 000 individuals was observed, and it was higher in the developed compared with the developing countries (1). Obviously, ischemic stroke is the major cause of disability associated with AF. When standard stroke risk factors were accounted for, AF was associated with a 4-to 5-fold increased risk of ischemic stroke (3) and about 15 percent of all people who have strokes have AF. Paroxysmal, persistent, and permanent AF all appeared to increase the risk of ischemic stroke to a similar degree (4). Although the risk ratio of stroke associated with AF did not vary substantively with advancing age, the proportion of strokes attributable to AF increased significantly; AF accounted for ≈1.5% of strokes in individuals 50 to 59 years of age and ≈23.5% in those 80 to 89 years of age (3). AF was also an independent risk factor for ischemic stroke severity, recurrence, and mortality (5), and it contributes to a higher morbidity and mortality compared with non-AF-related strokes (6).

Anticoagulation therapy has been shown to significantly reduce the risk for stroke in patients with AF. A meta-analysis of six placebo-controlled trials showed that warfarin significantly reduced stroke risk by 64% and mortality by 26% (7). Patients with AF who were not treated with anticoagulants had a 2.1-fold increase in risk for recurrent stroke and a 2.4-fold increase in risk for recurrent severe stroke (8). Despite the well-established evidences, warfarin is significantly underutilized for stroke prevention in at-risk patients with AF (9). Fortunately, the recent data from the Euro-Observational Research Program-AF (EORP-AF) registry demonstrated that adherence to the recommendations for oral anticoagulant use is improved, up to 80% overall (10). The EORP-AF registry had been initiated before the new oral anticoagulants (NOACs) were widely available in all European countries, and only 8% of patients were treated with the NOACs.

A potential barrier to warfarin use is the need for regular monitoring of international normalized ratio (INR) levels to ensure they are within the correct therapeutic range (11, 12). NOACs including a direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) act via direct and reversible inhibition of specific coagulation factors. They have a rapid onset and offset of action, and do not require routine monitoring of INR or other anticoagulation parameters. The correlation between their plasma concentrations and coagulation measures is good, resulting in predictable anticoagulant effects and making monitoring unnecessary. NOACs are either noninferior to or more effective than warfarin for reducing the risk of stroke or systemic embolism (13-16). All these NOACS have a favorable risk-benefit profile, with significant reductions in stroke, intracranial hemorrhage, and mortality, and with similar major bleeding as for warfarin (17). They would make the anticoagulant therapy more reliable and widely used. However, the increased risk of bleeding associated with anticoagulation still limits its use for stroke prevention even in the era of NOACs. Use of warfarin in patients with AF increases the risk of major bleeding and intracranial hemorrhage by 0.3-0.5% and 0.2% per year, respectively (18). Clinicians are often reluctant to prescribe warfarin to patients perceived to have a high risk of bleeding. Elderly patients with AF, who are at high risk of stroke and may derive the greatest clinical benefit from warfarin (19), are the least likely to receive warfarin, often due to perceived risks of bleeding (9).

Various stroke risk stratification schemes have been developed to quantify stroke risk in patients with AF and guide preventive treatment decisions for clinicians. The most widely used

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Accepted Date: 18.02.2014 **Available Online Date:** 19.03.2014
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DOI:10.5152/akd.2014.1271521

has been the $CHADS_2$ score, which estimates risk based on the presence of congestive heart failure, hypertension, age 75 years or greater, diabetes mellitus, and prior stroke or transient ischemic attack (TIA) (Table 1) (20). A revision of the $CHADS_2$ score, which dichotomizes age and incorporates vascular disease and female sex, has been developed to create the CHA_2DS_2-VASc (VA, vascular disease; Sc, sex category) score (Table 1) (21). Compared with $CHADS_2$, this scheme is better able to discriminate among individuals at the lowest risk. $CHADS_2$ and CHA_2DS_2-VASc scores are now widely used for the decision making about the anticoagulant therapy. Patients who score ≥1 by $CHADS_2$ or CHA_2DS_2-VASc are recommended to receive oral anticoagulant therapy unless major contraindications are present.

The each factor of $CHADS_2$ and CHA_2DS_2-VASc scheme represents the risk factor for ischemic stroke associated with AF. However, the mechanisms linking clinical risk factors to stroke are incompletely defined in patients with AF. Most of thrombi associated with AF originate in left atrial appendage (LAA) (22), suggesting the origin of thromboembolism. Therefore, the contribution of clinical factors to stroke could be largely mediated by LAA dysfunction and thrombosis. LAA contractile function is evaluated by measuring LAA emptying velocity on transesophageal echocardiography (TEE). Lower LAA empting velocity is associated with the higher incidence of LAA thrombosis. Spontaneous echo contrast (SEC), a dynamic smoke like signal within left atrium (LA) or LAA on TEE, represents a stasis of blood and a prothrombotic state, and it is a strong marker of thromboembolism (23, 24). Major clinical trials such as SPAF III demonstrated that presence of LAA thrombi, dense SEC, LAA peak emptying velocities ≤20 cm/s, and complex aortic plaques are independent predictors for thromboembolic events among echocardiographic risk factors (25-27).

Adding to these echocardiographic parameters assessing LAA function, left ventricular (LV) dysfunction could be related with ischemic stroke in patients with AF. Despite the original CHADS2 score did not include left ventricular (LV) systolic function as a predictive factor, the 2006 ACC/AHA/ESC guidelines for AF management allowed LV dysfunction as a risk factor for stroke (28). Moreover, the 2010 ESC guidelines included the moderate or severe LV systolic dysfunction, defined as an ejection fraction ≤40%, as a surrogate for heart failure in in the $CHADS_2$ scheme (29). The clinical risk factors included in the $CHADS_2$ and CHA_2DS_2-VASc score scheme, such as hypertension, diabetes, old age, congestive heart failure, vascular pathology, influence systolic and diastolic LV function directly or indirectly. Thus, the linkage between clinical risk factors and LAA thrombi may be mediated by LV systolic and diastolic dysfunction which could affect LA and LAA dynamics and pressure. In this issue of Anatolian Journal of Cardiology, Demirçelik et al. (30) investigated the effects of left ventricular diastolic dysfunction on LAA functions, spontaneous echo contrast (SEC) and thrombus formation in 58 patients with chronic AF and preserved LV systolic function. Among the study patients, those who showed LV diastolic dysfunction had lower LAA function indicated by lower LAA emptying velocity and lower LAA wall velocity. The prevalence of LAA thrombi was significantly higher in patients with diastolic dysfunction, and they tended to show higher SEC grade. Concluded that LV diastolic function could be associated with LAA dysfunction, and probably with LAA thrombosis, in patients with AF and preserved LV systolic function (30).

Table 1. $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Schemes

$CHADS_2$	
Congestive heart failure	1 point
Hypertension	
Age ≥75 years	
Diabetes mellitus	
Stroke, TIA, or systemic embolism	2 points
CHA_2DS_2-VASc	
Congestive heart failure	1 point
Hypertension	
Age 65 to 74 years	
Diabetes mellitus	
VAscular diseases*	
Sex Category (female)	
Age ≥75 years	2 points
Stroke, TIA, or systemic embolism	

TIA depicts transient ischemic attack
*Vascular diseases include myocardial infarction, perioheral arterial disease and aortic atheroma

LV diastolic dysfunction is associated with elevation of LV diastolic filling pressure, or elevated LA pressure. Elevated diastolic filling pressure attenuates appendage empting flow velocity in AF (31-33). LV filling pressure is well assessed by increased E/e' ratio, a ratio of early mitral valve flow velocity (E) divided by mitral annulus velocity during early diastole (e'), on echocardiography. E/e' ratio is the most reliable echocardiographic index to detect LV diastolic dysfunction, and it is so even during AF (34). Demirçelik et al. (30) demonstrated that, patients with diastolic dysfunction had higher E/e' ratio, indicating higher LV filling pressure in these patients. Increased E/e' ratio is associated with higher prevalence of LAA thrombi along with lower LAA empting velocity and higher rate of SEC in patients with AF (35). While E/e'>15 is widely used as a sign of elevated LV filling pressure and of LV diastolic dysfunction (36), the mean value of E/e' in the, diastolic-dysfunction group was 13.6. The prior study demonstrated that E/e'>13 was an optimal cut-off value for the prediction of LAA thrombi in AF (35), and the elevation of LV filling pressure could be associated with LAA thrombosis even if it remained within the normal limit.

Elevated filling pressure also could exert its effects through secondary changes in left atrial size. LA enlargement reflects severity and duration of LV diastolic dysfunction (37). Enlarged LA size is associated with higher incidences of SEC (38) and with LAA dysfunction (39). A recent substudy of ENGAGE AF-TIMI 48 revealed that majority of AF patients have both LA

enlargement and reduced LA contractile function, with an inverse relationship between them (40). With higher $CHADS_2$ scores, LA size increased and LA contractile function declined (40). In patients with chronic AF, atrial dilatation could be associated with increase in coagulate factors and endothelial dysfunction (41). Demirçelik et al. (30) showed no differences in LA size and LAA area between two groups. However, LA size measured on 2D-echocardiography might not correctly assess the changes in LA volume, and the possibility that morphological changes in LA was related with LAA thrombosis could not be fully excluded.

The present study has another clinical impact in the management of AF other than revealing the mechanisms of enhancement of LAA thrombosis in some fraction of patients. The study patients had normal ejection fraction, and LV diastolic dysfunction was associated with LAA thrombi even in these patients. Most of the studies regarding the clinical risk factors for ischemic stroke in AF have taken it granted for LV systolic dysfunction as a major cause of heart failure. However, almost half of the patients admitting hospital for heart failure have almost normal LV ejection fraction, which is now known as heart failure with preserved LV ejection fraction (HFpEF) (42). LV diastolic dysfunction is a major component of HFpEF, and patients with HFpEF are known to have a high incidence of AF. It is still not well elucidated whether HFpEF could increase the risk of ischemic stroke in patients with AF as well as heart failure with reduced ejection fraction (HFrEF) does. The present results suggested that LV diastolic dysfunction, and probably HFpEF, could be a novel risk factor for ischemic stroke in AF.

Presence of LAA thrombi is a well-established risk factor for ischemic stroke in patients with AF. However, the present study did not directly indicate the association between LV diastolic dysfunction and ischemic stroke in AF. Although no specific treatments for HFpEF are still established, blood pressure lowering could improve LV diastolic function in patients with hypertension (43). Antihypertensive therapy, by any kinds of drugs, could reduce the incidence of AF, but it is unclear whether it could reduce the risk of ischemic stroke in patients with AF through improvement of diastolic function or LA/LAA function. A small-scale, retrospective study like this one is not suitable for clarifying these important clinical issues. A large-scale, prospective study is required to fully elucidate the association between LV diastolic function and in patients with AF.

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