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 two-fold 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 has 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...
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 isch-
emic 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$_2$DS$_2$-VASc
(VA, vascular disease; Sc, sex category) score (Table 1) (21).
Compared with CHADS$_2$, this scheme is better able to discrimi-
nate among individuals at the lowest risk. CHADS$_2$ and CHA$_2$DS$_2$-
VASc scores are now widely used for the decision making about
the anticoagulant therapy. Patients who score $\geq 1$ by CHADS$_2$ or
CHA$_2$DS$_2$-VASc are recommended to receive oral anticoagulant
therapy unless major contraindications are present.

The each factor of CHADS$_2$ and CHA$_2$DS$_2$-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 emptying
velocity is associated with the higher incidence of LAA throm-
bosis. Spontaneous echo contrast (SEC), a dynamic smoke like
signal within left atrium (LA) or LAA on TEE, represents a stasis
of blood and a prothrombogenic 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 $\leq 20$ 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
CHADS$_2$ score did not include left ventricular (LV) systolic func-
tion 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 mod-
erate or severe LV systolic dysfunction, defined as an ejection
fraction $\leq 40\%$, as a surrogate for heart failure in the CHADS$_2$
scheme (29). The clinical risk factors included in the CHADS$_2$
and CHA$_2$DS$_2$-VASc score scheme, such as hypertension, dia-
betes, old age, congestive heart failure, vascular pathology, influ-
ence 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, Demircelik et al. (30) investi-
gated the effects of left ventricular diastolic dysfunction on LAA
functions, spontaneous echo contrast (SEC) and thrombus for-
mation in 58 patients with chronic AF and preserved LV systolic
function. Among the study patients, those who showed LV dia-
static dysfunction had lower LAA function indicated by lower

### Table 1. CHADS$_2$ and CHA$_2$DS$_2$-VASc Risk Stratification Schemes

<table>
<thead>
<tr>
<th>CHADS$_2$</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Hypertension</td>
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<td>Age $\geq$75 years</td>
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<td>Diabetes mellitus</td>
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<td>Stroke, TIA, or systemic embolism</td>
<td>2 points</td>
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<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td></td>
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<tr>
<td>Age 65 to 74 years</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Vascular diseases*</td>
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<tr>
<td>Sex Category (female)</td>
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<tr>
<td>Age $\geq$75 years</td>
<td>2 points</td>
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<tr>
<td>Stroke, TIA, or systemic embolism</td>
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TIA depicts transient ischemic attack

*Vascular diseases include myocardial infarction, peripheral arterial disease and aortic atheroma

LAA emptying velocity and lower LAA wall velocity. The preva-
ence 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).

LV diastolic dysfunction is associated with elevation of LV
diastolic filling pressure, or elevated LA pressure. Elevated
diastolic filling pressure attenuates appendage ejection flow veloc-
ity 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 echocar-
diography. E/e’ ratio is the most reliable echocardiographic index
to detect LV diastolic dysfunction, and it is so even during AF
(34). Demircelik et al. (30) demonstrated that, patients with dia-
stolic dysfunction had higher E/e’ ratio, indicating higher LV fill-
ing pressure in these patients. Increased E/e’ ratio is associated
with higher prevalence of LAA thrombi along with lower LAA
emptying velocity and higher rate of SEC in patients with AF (35).
While E/e’$>$15 is widely used as a sign of elevated LV filling pres-
sure and of LV diastolic dysfunction (36), the mean value of E/e’
in the, diastolic-dysfunction group was 13.6. The prior study
demonstrated that E/e’$>$13 was an optimal cut-off value for the
prediction of LAA thrombi in AF (35), and the elevation of LV fill-
ing 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 CHADS2 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.

Katsumi Iwakura, MD
Division of Cardiology, Sakurabashi Watanabe Hospital;
Osaka-Japan

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