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The prognostic significance of cardiac structure and function in atrial fibrillation: the ENGAGE AF-TIMI 48 Echocardiographic Substudy

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Abstract

Background—Atrial fibrillation (AF) is associated with increased risk for thromboembolism and death; however, the relationships between cardiac structure and function and adverse outcomes among individuals with AF are incompletely understood.

Methods—The ENGAGE AF –TIMI 48 study tested the once-daily oral factor Xa inhibitor edoxaban in comparison to warfarin for the prevention of stroke (ischemic or hemorrhagic) or systemic embolism in 21,105 subjects with nonvalvular AF and increased risk for thromboembolic events ($CHADS_2 \geq 2$). In a prospective substudy of 971 subjects who underwent transthoracic echocardiography at baseline, we used Cox proportional hazards models to evaluate the associations between cardiac structure and function and the risks for death and thromboembolism (ischemic stroke, TIA, or systemic embolism).

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Results—Over a median follow up of 2.5 years, 89 (9.2%) deaths and 48 (4.9%) incident thromboembolic events occurred in 971 subjects. In models adjusted for $CHADS_2$ score, aspirin use, and randomized treatment, larger LV end diastolic volume index (HR: 1.49 [95%CI: 1.16,1.91] per 1 SD [12.9 ml/m^2]) and higher LV filling pressures measured by E/′e (HR: 1.32 [95%CI: 1.08,1.61] per 1 SD [4.6]) were independently associated with increased risks for death. E/e′ > 13 significantly improved prediction of death beyond clinical factors alone. No features of cardiac structure and function were independently associated with thromboembolism in this population. Findings were similar when adjusted for CHA_2DS_2-VASc in place of $CHADS_2$.

Conclusions—In a contemporary population of patients with atrial fibrillation at increased risk for thromboembolic events, larger LV size and higher filling pressures were significantly associated with increased risk for death, but neither left atrial nor left ventricular measures were associated with thromboembolic risk. LV size and filling pressures may help identify AF patients at increased risk of death.

Keywords

Atrial fibrillation; ENGAGE AF-TIMI 48; Echocardiography; Thromboembolism; Stroke; Death

Introduction

Atrial fibrillation (AF) is common, increasing in prevalence, and is associated with increased risks for thromboembolism, stroke, and death.[1, 2] As non-fatal thromboembolism and stroke are associated with high morbidity, a key consideration in managing the AF patient includes thromboembolic risk assessment to inform antithrombotic recommendations.[3] Despite current risk prediction tools, such as $CHADS_2$ and CHA_2DS_2-VASc, decisions regarding whether to anticoagulate and choosing antithrombotic therapies in AF remain challenging.[1] Anticoagulation is associated with reduction in the risk of fatal and non-fatal strokes; however, thromboembolism accounts for a minority of deaths among AF patients.[2, 4, 5] Recent evidence demonstrates that death occurs more commonly in AF than stroke, and despite therapeutic advances in stroke prevention, mortality rates in AF have not substantially improved over the last decade.[2, 6] Therefore, a particular need exists to understand factors that contribute to the risk of death in AF, which may inform clinical management strategies aimed at decreasing mortality.

Cardiac structure and function in AF may be of prognostic value in refining thromboembolic and mortality risk assessments.[7-9] However, there are conflicting data regarding the relationships between cardiac structure and function in AF and the risk of thromboembolism.[10-13] Inconsistent findings may in part be related to limitations of prior echocardiographic studies which did not include contemporary measures of left ventricular (LV) and left atrial (LA) structure and function. To understand the impact of cardiac structure and function on the risks of thromboembolism and death, we evaluated the prognostic significance of cardiac structure and function in relation to thromboembolic events and all-cause mortality among subjects enrolled in the pre-specified echocardiographic sub-study of Effective aNticoaGulation with factor xA next Generation in AF-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48). We hypothesized

that left atrial dysfunction will be associated with increased risk of thromboembolic events and death among individuals with atrial fibrillation.

Material and methods

Study Population

ENGAGE AF–TIMI 48 was a multinational, randomized (1:1:1), double-blind, double-dummy non-inferiority design trial comparing the efficacy and safety of two dosing regimens of once-daily edoxaban (high and low dose with dose reductions for patients with decreased clearance of edoxaban) versus warfarin titrated to an INR of 2.0 to 3.0 in subjects with a history of AF.[14] The study included AF subjects at moderate to high risk for thromboembolic events based upon a $CHADS_2 \geq 2$. Inclusion and exclusion criteria and the primary results demonstrating non-inferiority of edoxaban compared with warfarin for the prevention of stroke or systemic embolism have been reported.[14, 15] Briefly, eligible subjects were men or women ≥ 21 years old with a history of AF of any duration documented by an electrocardiogram within the prior 12 months and in whom anticoagulation was indicated. Key exclusion criteria were: AF due to reversible causes, severe renal dysfunction (creatinine clearance < 30 ml/min), high bleeding risk, moderate or severe mitral stenosis, or a mechanical valve in any position. Mitral regurgitation was not excluded. Rate or rhythm control strategy was not specified by the study protocol and was at the discretion of the local physician. The study protocol complied with the Declaration of Helsinki and was approved by institutional review boards at each site. Written informed consent was obtained in all patients.

The prospectively designed echocardiographic sub-study of ENGAGE AF-TIMI 48 was performed at 133 sites worldwide between 2009 and 2011. The echocardiographic procedures, protocol, and results of a baseline cross-sectional analysis of the ENGAGE AF-TIMI 48 Echocardiographic sub-study population prior to the availability of longitudinal outcomes have been previously reported.[8] In the current report, the same echocardiographic sub-study population is now examined with regards to longitudinal associations between baseline cardiac structure and function and the outcomes of thromboembolism and death over a median of 2.5 years of follow up. Subjects were invited prior to randomization to voluntarily participate with echocardiographic imaging obtained within the first week after randomization. Standard 2D and Doppler transthoracic echocardiography was performed with images sent to the echocardiography core laboratory at Brigham and Women's Hospital, Boston, MA. Conventional echocardiographic analyses were performed by technicians blinded to clinical information and treatment assignment, with all study measurements confirmed by a board certified cardiologist and echocardiographer.[8] Reproducibility of echocardiographic measurements was good to excellent with an intra-observer intraclass correlation coefficient of 0.95 (0.91–0.99) and inter-observer intraclass correlation coefficient of 0.84 (0.75–0.93).[8]

Echocardiographic analyses

Echocardiography was performed according to American Society of Echocardiography guidelines.[8, 16, 17] LV volumes and ejection fraction (LVEF) were calculated by the

modified Simpson's method. LV mass was calculated from LV linear dimensions using the ASE recommend formula ($0.8 \times (1.04[(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]) + 0.6$ g) and indexed to body surface area, with LV hypertrophy (LVH) defined as LV mass index (LVMI) >115 g/m^2 in men or >95 g/m^2 in women. LV geometry was categorized as normal (relative wall thickness ≤0.42 and no LVH) or abnormal (relative wall thickness >0.42 or LVH).

LA diameter was the 2D anterior-posterior length in the parasternal long axis view. LA maximum volume was measured by the modified Simpson's method using apical 4- and 2-chamber views at the end-systolic frame preceding mitral valve opening, and was indexed to body surface area to derive LA volume index (LAVI). Similarly, LA minimum volume was measured at the end diastolic frame preceding mitral valve closure. LA emptying fraction was calculated as: 100 × (maximum volume – minimum volume)/maximum volume (Figure 1).[18, 19]

Early transmitral velocity (E) was measured by pulsed wave Doppler from the apical 4-chamber view with the sample volume positioned at the tip of the mitral leaflets. Peak lateral and septal mitral annular early relaxation velocities (e′) were assessed using tissue Doppler imaging. LV filling pressures were estimated by E wave divided by average e′ velocities (E/e′). Right ventricular systolic pressure was calculated from the peak tricuspid regurgitant velocity using the simplified Bernoulli equation and assuming a right atrial pressure of 10 mmHg. Final values for all parameters were taken as the mean of measurements from three cardiac cycles.

Outcomes

The primary endpoints for this analysis were time to a) thromboembolic event (defined as ischemic stroke, transient ischemic attack (TIA) or systemic embolic event (SEE)), and b) death from any cause. All events were adjudicated by an independent clinical end-point committee whose members were blinded to study assignment. The median follow up period was 2.5 years (IQR: 2.3, 2.8).

Statistical methods

Subjects were stratified into groups according to those who did and did not have a thromboembolic event in follow up or those who were alive or dead. Summary statistics for clinical characteristics and cardiac structure function were calculated with results presented as medians (interquartile ranges) and counts (percentages), for continuous and categorical data, respectively. Statistical comparisons were made between subjects who did or did not have the outcome of interest in follow up using χ^2, Fisher's exact, or Wilcoxon rank sum tests, as appropriate. Incidence rates for thromboembolism and death per 100 person years were calculated. Multivariable Cox proportional hazard models were used to assess the association between covariates and the risk of thromboembolism and death. The echocardiographic substudy was not powered to assess effect modification of treatment (warfarin vs. high dose edoxaban vs. low dose edoxaban) by features of cardiac structure and function on the outcomes of thromboembolism or death. However, to control for treatment assignment in analyzing the association between cardiac structure and function

and outcomes, randomization was included as a covariate in multivariable models. To examine the incremental value of cardiac structure and function on the prediction of the outcomes beyond clinical factors, receiving operating curve analyses were performed. All analyses were performed using Stata 11.2 (Stata Corp., College Station, Tx) with p values < 0.05 considered statistically significant.

Results

Clinical Characteristics

Over a median follow up of 2.5 years (IQR 2.3, 2.8), incident thromboembolic events occurred in 48 subjects (Table 1). Thromboembolic events were more frequent among subjects with higher $CHADS_2$ scores. The frequency of thromboembolic events did not differ according to paroxysmal, persistent, or permanent AF. Aspirin use was significantly lower among subjects who had a thromboembolic event as compared to those who did not. In contrast, there was no significant difference with regards to the occurrence of thromboembolism during follow up in relation to randomization to warfarin or edoxaban.

A total of 89 deaths occurred over the follow up period (Table 1). Death was more frequent among subjects with higher $CHADS_2$ score. Vascular disease and chronic kidney disease were also more common among subjects who died. Aspirin use did not significantly differ between those who were alive versus dead at follow up. Similarly, no significant difference was observed with regards to death in relation to randomization to warfarin or edoxaban.

Cardiac Structure and Function

Left ventricular size, mass, ejection fraction, and filling pressures did not significantly differ between subjects who had a thromboembolic event in follow up as compared with those who did not (Table 2). LA size and function were also similar between these two groups.

In contrast, subjects who died, as compared with survivors, had significantly larger LV size and mass, with lower ejection fractions as well (Table 2). LA size was significantly larger among subjects who died and LA function, as assessed by emptying fraction, was also significantly lower. LV filling pressures, measured by E/e′, were significantly higher among subjects who died as compared with those who survived.

Risks of thromboembolism and death

Thromboembolism occurred in 4.9% of the study population at a rate of 2.0% per year (95% CI: 1.5,2.7). Death occurred in 9.2% of subjects at a rate of 3.6% per year (95%CI: 2.9,4.5). Cardiovascular death accounted for the majority (72%) of deaths, of which 53%, 16%, and 16% were due to sudden cardiac or unwitnessed death, heart failure, and hemorrhagic or ischemic stroke, respectively.

In multivariable adjusted models, no features of cardiac structure and function were associated with thromboembolic risk independent of $CHADS_2$ score (Figure 2). In contrast, larger LV end diastolic volume index (LVEDVI) (HR: 1.49, 95%CI 1.16, 1.91) and higher E/e′ (HR: 1.32, 95% CI 1.08, 1.61) were both significantly and independently associated with increased risk for death.

In an additional analysis, CHA_2DS_2-VASc was included in the model in place of $CHADS_2$ and the significant associations between LVEDVI (HR: 1.49, 95%CI 1.16, 1.91) and E/e′ (HR: 1.31, 95%CI 1.07, 1.61) with death did not appreciably change.

Sensitivity analyses

We performed several additional analyses to examine the influence of age as continuous variable, sex, creatinine clearance, rhythm at the time of echocardiography, type of atrial fibrillation (paroxysmal, persistent, or permanent), and mitral regurgitation on each of the outcomes. Inclusion of these covariates did not change the significant associations between LVEDVI, E/e′, and death (data not shown). Similarly, inclusion of these covariates did not change the findings for thromboembolism. In addition, age, sex, creatinine clearance, rhythm at the time of echocardiography, type of atrial fibrillation, and severity of mitral regurgitation were not significantly associated with risk of thromboembolism or death ($P > 0.05$ for all).

Left atrial anterior-posterior diameter

LA enlargement was defined as an anterior-posterior diameter ≥ 4.0 cm and included in univariable and multivariable adjusted Cox models. Using this definition, LA enlargement was not a significant predictor of thromboembolism (HR: 0.39, 95%CI 0.11, 1.38) or death (HR: 1.16, 95%CI 0.60, 2.27).

Incremental value of LVEDVI or E/e′ on the prediction of death

In receiver operating curve analyses, addition of E/e′ > 13 to clinical factors significantly improved prediction of death (AUC 0.71, 95% CI 0.64, 0.77) compared with a model based upon clinical factors alone (AUC 0.67 95% CI 0.60, 0.73), $P = 0.031$. In contrast, the inclusion of left ventricular enlargement, defined as a LVEDVI > 75 ml/m^2, did not substantially improve prediction of death over clinical variables alone, $P = 0.70$ (Figure 3).

Discussion

Among 971 subjects with AF and $CHADS_2 \geq 2$ enrolled in the ENGAGE AF-TIMI 48 echocardiographic sub-study, we found that death was a more frequent event than thromboembolism over a median of 2.5 years of follow up. Features of cardiac structure and function, including larger LV size and higher LV filling pressures were significantly and independently associated with increased risks for death. Additionally, E/e′ > 13 significantly improved prediction of death beyond clinical factors alone. In contrast, no conventional features of cardiac structure and function associated with higher or lower risk of thromboembolic events in follow up.

AF patients are at increased risk for stroke and death. Although death is a more frequent event than stroke, relatively less attention has been given to predicting the risk of death in AF.[2, 4, 20, 21] We found that increased LVEDVI and E/e′ were significantly associated with increased risks of death, independent of $CHADS_2$ or CHA_2DS_2-VASc. E/e′ has been previously validated as a non-invasive measure of LV filling pressures in AF patients and retrospective analyses indicate that higher E/e′ is associated with an increased risk for death.

[22, 23] Our findings in this relatively large (n=971) multicenter prospective echocardiographic sub-study validate the results of the prior smaller retrospective studies (ranging in size from 27 to 230 patients) and extend them by demonstrating the incremental value of E/e′ > 13 beyond clinical factors for the prediction of death. We also demonstrated that increased LV size is associated with all-cause mortality. Larger LV size and higher LV filling pressures may be indicative of volume overload conditions, such as heart failure or chronic kidney disease. The complex associations between AF and heart failure are well recognized and heart failure may be an important mediator of the risk of sudden cardiac death among AF patients.[2, 24-26] Indeed, sudden cardiac death and heart failure were the leading causes of cardiovascular death in this cohort. We also found a non-significant trend towards higher mortality among AF patients with prevalent heart failure. Moreover, the association between larger LV size and higher LV filling pressures and mortality was independent of creatinine clearance in this population without severe renal dysfunction. Therefore, our findings may provide additional insights into markers of and contributors to death in AF. Our findings also emphasize the clinical importance of measuring and reporting LV size and filling pressures among AF patients. Greater attention to LV size and, in particular, filling pressures may not only help clinicians risk stratify AF patients, but also inform therapies directed at reverse LV remodeling (e.g. renin-angiotensin-aldosterone axis inhibitors and/or beta-blockers) and reducing filling pressures (e.g. diuretics) that may be of benefit, although these hypotheses remain to be formally tested.

In contrast to mortality, conventional features of cardiac structure and function were not associated with either higher or lower thromboembolic risk among moderate to high risk AF subjects based upon $CHADS_2$ score. This may in part be explained by the relatively small number of thromboembolic events in follow up that may have limited statistical power. However, these findings are consistent with results from another large study of cardiac structure and function in AF.[13] Additionally, as the ENGAGE AF-TIMI 48 study enrolled subjects with a $CHADS_2$ score ≥ 2, the findings may indicate that among AF patients already at moderate to high risk based upon clinical factors, cardiac structure and function does not independently predict increased risk for thromboembolic outcomes. Conversely, no feature of cardiac structure and function, e.g. smaller LA size or higher LVEF, was associated with lower thromboembolic risk sufficient to alter management recommendations regarding whether to anticoagulate patients with a $CHADS_2$ score ≥ 2. Whether cardiac structure and function is of prognostic significance among lower risk AF patients, i.e. $CHADS_2 \leq 1$ remains to be prospectively tested.

We previously demonstrated that larger LA size, abnormal LV geometry, and elevated LV filling pressures were significantly associated with higher $CHADS_2$ score as a marker of stroke risk in this population.[8] However, there was greater power to identify differences with $CHADS_2$ than to detect differences in actual thromboembolic outcomes.[8] The $CHADS_2$ score has also been shown to be predictive of death in addition to stroke; therefore, our previous findings may have reflected the relationship between cardiac structure and function and mortality risk.[27] The lack of significant association between features of cardiac structure and function and thromboembolic risk in this population may also be related to the limitations of transthoracic echocardiography to characterize the left atrial appendage, which is believed to be a source of thrombus in AF.[28]

Although we evaluated a relatively large contemporary AF population, limitations should be noted. The irregular rhythm of AF will lead to beat to beat variability in echocardiographic assessment; however, we averaged measures of cardiac structure and function over multiple cardiac cycles. Though we did not directly assess the correlation between E/e′ and invasively measured left ventricular filling pressures, previous literature supports the high correlation between E/e′ and left ventricular end diastolic pressure in atrial fibrillation.[17, 23] In this echocardiographic sub-study of ENGAGE AF-TIMI 48, we did not find that conventional volumetric measures of left atrial structure and function were associated with the clinical outcomes of thromboembolism and death. The lack of statistically significant association may reflect the insensitivity of volume based left atrial measures for predicting these adverse outcomes or type II error. We cannot exclude that unmeasured characteristics of left atrial structure and function may be associated with adverse clinical outcomes among individuals with atrial fibrillation. For example, novel measures of cardiac mechanics, such as strain and strain rate from speckle tracking echocardiography, may provide additional prognostic information and is a future direction.[29] Furthermore, due to ENGAGE AF-TIMI 48 eligiblity criteria, we could not study whether left atrial structure and function is associated with prognosis among lower risk, i.e. $CHADS_2 < 2$, or unanticoagulated patients with atrial fibrillation. The analysis was based upon cardiac structure and function at baseline and does not account for changes over time that may contribute to thromboembolic risk. Right ventricular function was not assessed. Information regarding the duration of atrial fibrillation was not available. By design, ENGAGE AF-TIMI 48 enrolled a moderate to high risk AF population ($CHADS_2 \geq 2$) and therefore our analysis does not include the entire spectrum of AF patients, particularly younger patients. Similarly, we evaluated AF subjects who volunteered to participate in an echocardiographic substudy of the larger ENGAGE AF-TIMI 48 clinical trial in which all subjects were anticoagulated (median time in therapeutic range for those randomized to warfarin was 72%) and therefore due to inclusion and exclusion criteria the results may not be applicable to the broader AF population.

Conclusions

In a moderate to high risk population of AF subjects enrolled in the echocardiographic sub-study of ENGAGE AF-TIMI 48, we found that measures of cardiac structure and function were associated with an increased risk of death, which was a more frequent event than thromboembolism, for which these measures were not predictive. LV size and filling pressures may help identify AF patients at increased risk of death and could be targets for therapies directed at improving survival.

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Abbreviations

AF	Atrial fibrillation

LV	Left ventricular
LA	Left atrial
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
LVH	Left ventricular hypertrophy
LAVI	Left atrial volume index
LVEDVI	Left ventricular end diastolic volume index

Highlights

- In 971 moderate to high risk subjects ($CHADS_2 \geq 2$) with atrial fibrillation enrolled in the echocardiographic sub-study of ENGAGE AF-TIMI 48, death was a more frequent than thromboembolism
- Larger left ventricular size and higher filling pressures were associated with increased risks of death
- Neither left atrial nor left ventricular measures associated with thromboembolic risk
- LV size and filling pressures may help identify AF patients at increased risk of death

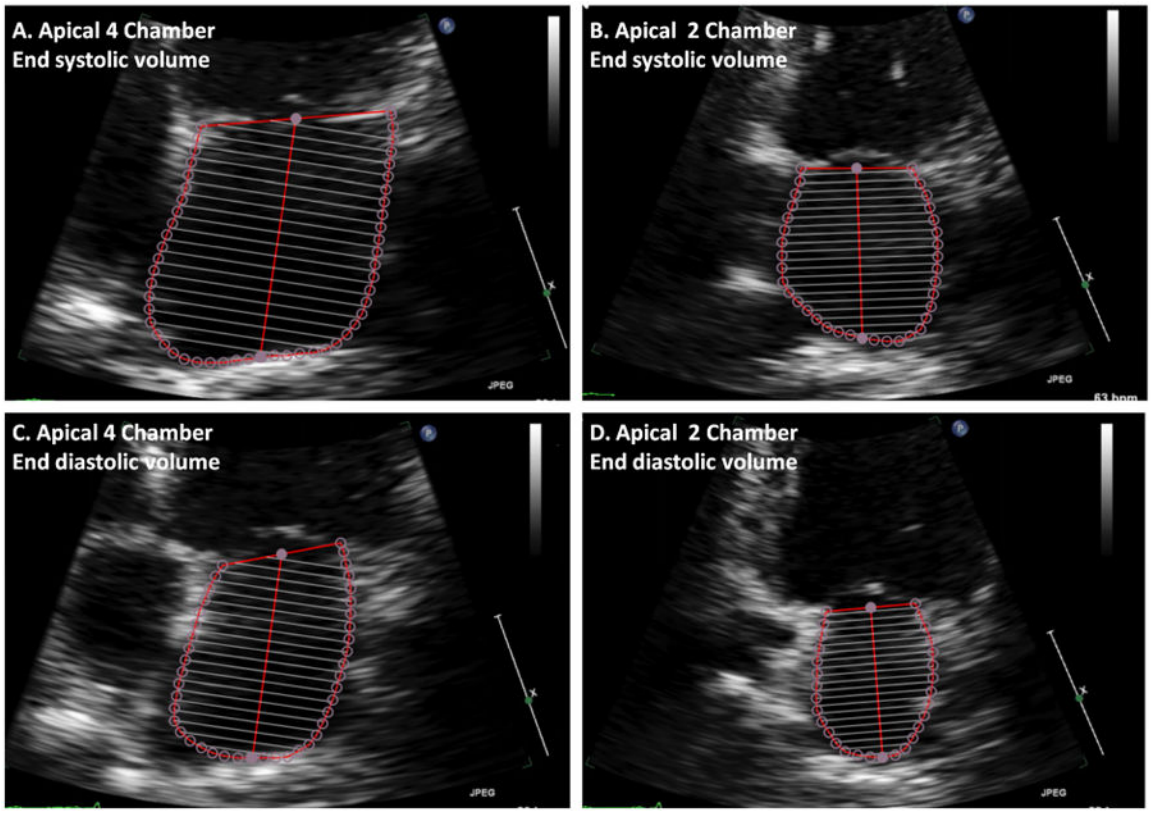


Figure 1.

Calculation of left atrial emptying fraction from the apical 4 and 2 chamber views.

Left atrial volume is calculated by the method of disks from focused apical 4 and 2 chamber views at maximum (end ventricular systole) and minimum (end ventricular diastole) volume. The left atrial emptying fraction is calculated from these volumes as 100 × (maximum – minimum)/maximum. In this example, the left atrial emptying fraction is 54%.

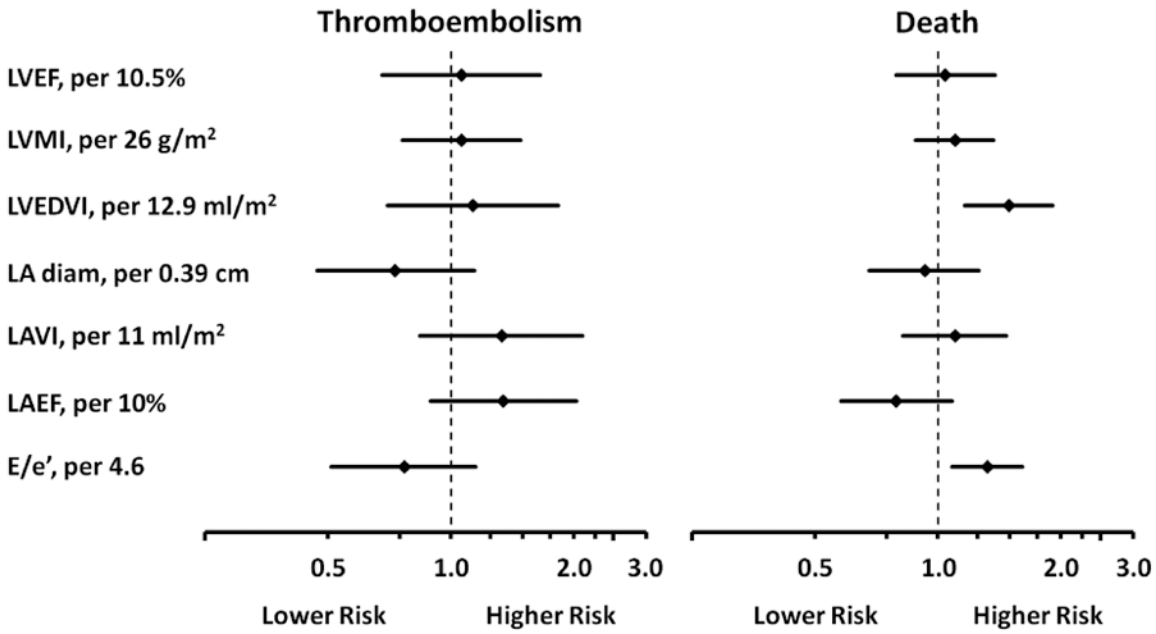
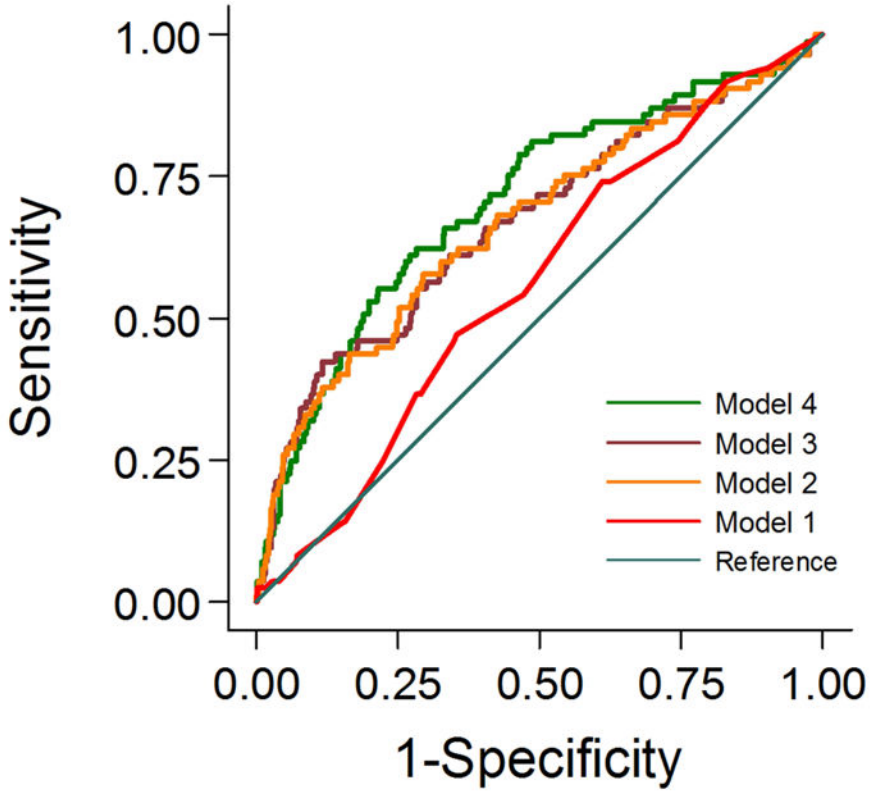


Figure 2.

Forest plot of multivariable adjusted hazard ratios for the risk of thromboembolism or death according to features of cardiac structure and function among subjects with atrial fibrillation in the ENGAGE AF-TIMI 48 echocardiography sub-study.

Multivariable adjusted hazard ratios (point) and 95%CI (line) from Cox proportional hazards models. Covariates included $CHADS_2$ score, aspirin use at baseline, randomization to warfarin, edoxaban (low dose), edoxaban (high dose), and all of the features of cardiac structure and function shown. Hazard ratios reflect risk per 1 standard deviation increase. LA diam = left atrial diameter. Other abbreviations as in Table 2.



Model	Covariates	AUC (95% CI)
1	$CHADS_2$, randomization, ASA	0.56 (0.50,0.62)
2	HF, HTN, Age, DM, Stroke, Vasc. dis., sex, Cr Cl, randomization, ASA	0.67 (0.60,0.73)
3	Model 2 + LVEDVI > 75 ml/m^2	0.67 (0.60,0.74)
4	Model 2 + E/e' > 13	0.71 (0.64,0.77)

Figure 3.

The incremental value of E/e′ beyond clinical factors in the prediction of death among subjects with atrial fibrillation in the ENGAGE AF-TIMI 48 echocardiography substudy. Receiver operating curve analyses for the incremental value of left ventricular size and filling pressures compared with clinical factors for the prediction of death. The inclusion of left ventricular end diastolic volume index > 75 ml/m^2 did not significantly improve prediction of death (P = 0.70 for model 3 vs. model 2). In contrast, addition of E/e′ > 13 to clinical factors did significantly improve prediction of death (P = 0.031 for model 4 vs. model 2).

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Table 1

Clinical characteristics of atrial fibrillation subjects of the ENGAGE AF-TIMI 48 echocardiography substudy stratified according to thromboembolic event or death in follow up

Characteristic	No TE N = 923	+ TE N = 48	p	Alive N = 882	Dead N =89	p
Age, yrs	73 (65,79)	74.5 (67,79)	0.53	73 (65,78)	76 (66,82)	0.031
Sex, male	606 (66)	31 (65)	0.88	571 (65)	66 (74)	0.075
Caucasian	850 (92)	46 (96)	0.34	811 (92)	85 (96)	0.23
$CHADS_2$			0.045			0.001
2	451 (49)	24 (50)		440 (50)	35 (39)	
3	275 (30)	8 (17)		248 (28)	35 (39)	
4	147 (16)	9 (19)		143 (16)	13 (15)	
5-6	50 (5)	7 (15)		51 (6)	6 (7)	
Heart Failure	499 (54)	22 (46)	0.27	465 (53)	56 (63)	0.066
Hypertension	872 (94)	45 (94)	0.83	833 (94)	84 (94)	0.98
Age > 75 yrs	418 (45)	24 (50)	0.52	394 (45)	48 (54)	0.094
Diabetes mellitus	326 (35)	20 (42)	0.37	306 (35)	40 (45)	0.054
Stroke/TIA	240 (26)	18 (38)	0.08	237 (27)	21 (24)	0.51
Vascular Disease	389 (42)	25 (52)	0.18	366 (42)	48 (55)	0.018
Smoking, current	96 (10)	4 (8)	0.81	89 (10)	11 (12)	0.50
Obese (BMI > 30 kg/m^2)	388 (42)	19 (40)	0.74	371 (42)	36 (40)	0.77
Baseline heart rate, bpm	72 (63,81)	74 (63,81)	0.66	72 (62,80)	73 (67,82)	0.17
CKD (CrCl 30- 60 ml/min)	306 (34)	19 (40)	0.40	285 (33)	40 (47)	0.007
Type of AF			0.22			0.98
Paroxysmal	298 (32)	21 (44)		294 (33)	25 (28)	
Persistent	196 (21)	7 (15)		183 (21)	20 (22)	
Permanent	429 (46)	20 (42)		405 (46)	44 (49)	
BMI, kg/m^2	29 (26,33)	29 (25,34)	0.68	29 (26,33)	28 (25,32)	0.15
Cr Cl, ml/min	72 (55,92)	64 (47,93)	0.15	72 (56,92)	63 (41,88)	0.003
Anti-arrhythmic med	177 (19)	9 (19)	0.94	173 (20)	13 (15)	0.32
ACEI or ARB	538 (58)	27 (56)	0.77	512 (58)	53 (60)	0.82
Beta-blocker	624 (68)	33 (69)	0.87	594 (67)	63 (71)	0.55

Characteristic	No TE N = 923	+ TE N = 48	p	Alive N = 882	Dead N =89	p
Diuretic	923 (100)	48 (100)	n/a	882 (100)	89 (100)	n/a
Aspirin use at baseline	285 (31)	8 (17)	0.037	271 (31)	22 (25)	0.24
Randomized			0.17			0.69
warfarin	316 (34)	11 (23)		297 (34)	30 (34)	
Edoxaban (low)	315 (34)	22 (46)		303 (34)	34 (38)	
Edoxaban (high)	292 (32)	15 (31)		282 (32)	25 (28)	

Data shown as count (%) or median (IQR). TE = thromboembolic; TIA = transient ischemic attack; BMI = body mass index; CKD = chronic kidney disease; Cr Cl = creatinine clearance.

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Table 2

Cardiac structure and function in atrial fibrillation subjects in the ENGAGE AF-TIMI 48 echocardiography substudy stratified according to thromboembolic event or death in follow up

Characteristic	No TE N = 923	+ TE N = 48	p	Alive N = 882	Dead N = 89	p
Sinus rhythm at echo	298 (32)	23 (48)	0.028	295 (33)	26 (29)	0.48
Left ventricular						
LVEF, %	59 (53,61)	59 (57,61)	0.061	59 (54,61)	57 (44,60)	0.003
LVEF < 50%	210 (23)	7 (15)	0.19	185 (21)	32 (36)	0.001
LVEDVI, ml/m^2	56 (51,62)	57 (53,63)	0.32	56 (51,62)	58 (53,69)	0.010
LV mass, g	136 (113,172)	145 (120,178)	0.50	135 (112,171)	151 (125,183)	0.003
LVMI, g/m^2	68 (58,88)	72 (60,91)	0.33	68 (58,88)	76 (63,98)	0.003
Abnl LV geometry *	258 (28)	18 (38)	0.15	252 (29)	24 (27)	0.75
Left atrial						
LA diameter, cm	3.6 (3.4,3.8)	3.5 (3.4,3.8)	0.17	3.6 (3.4,3.8)	3.7 (3.4,4.0)	0.055
LAVI, ml/m^2	33 (26,39)	33 (27,38)	0.95	33 (26,39)	34 (28,45)	0.031
LAVI > 34 ml/m^2	413 (45)	19 (40)	0.55	386 (44)	46 (52)	0.18
LA emptying fraction, %	38 (30,45)	40 (33,49)	0.12	38 (31,46)	35 (27,43)	0.015
Doppler						
TDI e′ avg, cm/s	7.7 (6.2,9.1)	7.2 (6.6,9.0)	0.65	7.7 (6.2,9.1)	7.1 (5.9,9.1)	0.18
E/e′ avg	10.7 (8.6,13.8)	10.2 (7.9,12.4)	0.22	10.6 (8.5,13.5)	12.3 (9.3,16.7)	0.004
E/e′ ≥ 13	403 (44)	20 (42)	0.88	367 (42)	56 (63)	<0.001
≥ Moderate MR	93 (11)	6 (13)	0.69	85 (10)	14 (17)	0.07
**RVSP, mmHg	32 (29,36)	34 (28,39)	0.57	32 (28,36)	36 (30,42)	<0.001

Data shown as count (%) or median (IQR). TE = thromboembolic; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end diastolic volume index; LVMI = left ventricular mass index; Abnl = abnormal; LA = left atrial; LAVI = left atrial volume index; TDI = tissue Doppler imaging; e′ = mitral annular early diastolic velocity; E/e′= transmitral E wave velocity/e; MR = mitral regurgitation'.

*Abnormal LV geometry defined as hypertrophy or concentric remodeling.

**RVSP measurable in 587/971 (60%) of subjects.