Prognostic value of trans-thoracic echocardiography in patients with acute stroke and atrial fibrillation: findings from the RAF study

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Abstract

Background and purposes: Anticoagulant therapy is recommended for the secondary prevention of stroke in patients with atrial fibrillation (AF). The identification of patients at high risk for early recurrence, which are potential candidates to prompt anticoagulation, is crucial to justify the risk of bleeding associated with early anticoagulant treatment. The aim of this study was to evaluate in patients with acute ischemic stroke and AF the association between findings at trans-thoracic echocardiography (TTE) and 90 day recurrence.

Methods: In consecutive patients with acute ischemic stroke and AF, TTE was performed within 7 days from hospital admission. Study outcomes were recurrent ischemic cerebrovascular events (stroke or TIA) and systemic embolism.

Results: 854 patients (mean age 76.3±9.5 years) underwent a TTE evaluation; 63 patients (7.4%) had at least a study outcome event. Left atrial thrombosis was present in 11 patients (1.3%) among whom 1 had recurrent ischemic event. Left atrial enlargement was present in 548 patients (64.2%) among whom 51 (9.3%) had recurrent ischemic events. The recurrence rate in the 197 patients with severe left atrial enlargement was 11.7%. On multivariate analysis, the presence of atrial enlargement (OR=2.13; 95% CI 1.06-4.29, p=0.033) and CHA_2DS_2-VASc score (OR 1.22; 95% CI 1.04-1.45, p=0.018, for each point increase) were correlated with ischemic recurrences.

Conclusion: In patients with AF-associated acute stroke, left atrial enlargement is an independent marker of recurrent stroke and systemic embolism. The risk of recurrence is accounted for by severe atrial enlargement. TTE-detected left atrial thrombosis is relatively uncommon.

Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an elevated risk of ischemic stroke and systemic thromboembolism. After an acute stroke, patients with AF have a high risk of early recurrence that is about 8% within 90 days from the acute event (1).

Anticoagulant therapy is effective for the secondary prevention of stroke in patients with AF. The balance between the risk of recurrence and bleeding associated to anticoagulant therapy for any given patient remains unclear. The identification of patients at high risk for early recurrence, which are potential candidates to prompt anticoagulation, is crucial to justify the risk of bleeding associated with early anticoagulant treatment.

Echocardiography, transthoracic (TTE) or less commonly transesophageal (TEE), is included in the work-up of patients with AF and stroke. In these patients, echocardiography detected left atrial thrombosis supports early anticoagulation (2). Likewise, in patients with acute stroke, left atrial enlargement, has been associated with the risk of stroke recurrence (3).

The aim of this study was to evaluate the potential association between TTE findings in the early stage of cerebral ischemia (within 7 days from hospital admission) and the risk of 90-day thromboembolic recurrence in patients with acute ischemic stroke and AF.

Methods

Patients

Data for this analysis were extracted from the database of a prospective multicentre study which enrolled consecutive patients with acute stroke and AF (the RAF study) (1). This study, carried out between January 2012 and March 2014, enrolled 1,029 consecutive patients in 29 Stroke Units from Europe and Asia.

On admission, the severity of acute stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS); all investigators were certified about the use of this scale.

AF was classified as paroxysmal (episodes terminating spontaneously within 7 days), persistent (episodes lasting more than 7 days requiring pharmacologic and/or electrical stimulation), or permanent (persisting for more than 1 year, either because cardioversion failed or was not attempted).

Risk factors

Data on known stroke risk factors were collected as reported in the main paper (1).
A cerebral computed tomography (CT) or magnetic resonance (MR) was performed on admission in all patients to exclude intracranial hemorrhage. A second cerebral CT scan or MR was performed 48-72 h from stroke onset. The sites and sizes of the qualifying infarcts were determined based on standard templates (4,5) as follows: (a) small, when a lesion was ≤1.5 cm in the anterior or posterior circulation, (b) medium, when a lesion was in a cortical superficial branch of middle cerebral artery [MCA], in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery [PCA], in the PCA branch or in a cortical superficial branch of the anterior cerebral artery [ACA]), (c) large anterior, when a lesion involved the complete territory of MCA, PCA, or ACA, in 2 cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than 1 artery territory [eg, MCA associated to ACA territories]), (d) large posterior, when a lesion was ≥1.5 cm in the brain stem or cerebellum (6).

Echocardiogram evaluation

TTE was performed within 7 days form stroke onset by a local cardiologist using a standardized protocol. Patients were imaged in the left lateral decubitus. Images were obtained using a 3.5 MHz transducer, at a depth of 16 cm in the parasternal (standard long- and short-axis images) and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data, triggered to the QRS complex,

were saved in cine loop format. Pulsed and continuous wave Doppler data were also stored digitally.

TTE analysis included the presence of: 1) intra-cardiac thrombus; 2) left atrial enlargement; 3) mitral valve stenosis or regurgitation; 4) aortic valve stenosis or regurgitation; 5) tricuspidal valve stenosis or regurgitation; 6) dilated cardiomyopathy with left ventricular ejection ≤40%. Presence of pacemaker, biological or mechanical valve (mitral or aortic) was also assessed.

The presence of an intra-cardiac thrombus was diagnosed by the presence of an echo-dense mass distinct from the endocardium in any cardiac cavity (7).

Left atrial enlargement was defined following the American Society of Echocardiography guidelines measuring the left atrial diameter or volume taking into account the difference between sexes (8). The severity of atrial enlargement was defined according the definitions described in table 1.

Mitral, aortic and tricuspid stenoses or regurgitations were dichotomized as absent or present (mild/moderate/severe) following the definitions of published guidelines (9,10).

Evaluation of outcome

Patients were followed-up prospectively by office or telephone interviews. Study outcome was the composite of recurrent ischemic cerebrovascular events (stroke or TIA) and symptomatic systemic embolisms. Recurrent ischemic stroke was defined as the sudden onset of a new focal neurological deficit of vascular origin in a site consistent with the territory of a major cerebral artery and after exclusion of cerebral hemorrhage at neuroimaging. TIA was defined as a transient episode of neurological dysfunction caused by focal brain ischemia without acute infarction. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ confirmed by imaging, surgery, or autopsy. The diagnosis of systemic embolism was independently adjudicated by vascular surgeons.

Statistical analysis

Differences in the characteristics of patients with or without outcome events were tested using χ-square test. Correlations between TTE characteristics and risk of recurrent ischemic events were sought by multiple logistic regression analysis. The variables included in the model other than the TTE characteristics were the type of AF, CHA_2DS_2-VASc score, cardiovascular risk factors, reperfusion therapy, the severity of stroke on admission according to NIHSS score, the presence of pacemaker, biological or mechanical valve, anti-thrombotic treatment and size of the lesion.

The relationship between the recurrent ischemic events and the TTE characteristics, correlated to outcome on multivariate analysis, were also explored with Cox proportional hazard models. The Cox model provides an estimate of the effect of TTE characteristics on recurrent ischemic events after adjusting for: lesion sizes, age, sex, type of AF, NIHSS on admission, anticoagulant treatment, the presence of pacemaker and the histories of hypertension, diabetes, previous stroke/TIA and congestive heart failure.

Results

Overall, 1,037 consecutive patients were included in the study. Of these, 8 patients were excluded for incomplete data while 1,029 patients were included in the analysis; of these, 854 patients had a TTE evaluation. The 175 patients did not undergo TTE evaluation for the following reasons: 34 (19.4%) early death, 86 (49.2%) severe stroke and 55 (31.4%) for unknown reasons. The characteristics of the patients with and without TTE evaluation are summarized in table 2. Patients without TTE evaluation were older, with a more severe stroke and with more cardiovascular risk factors.

Mitral valve disease was present in 360 patients (42.2%; 275 regurgitations and 85 stenosis) while aortic valve disease was present in 230 patients (24.9%; regurgitation in 47 and stenosis in 183). In 168 patients (19.7%), mitral valve disease was associated

with aortic valve disease. Intra-cardiac thrombosis, all in left atrium, was present in 11 patients (1.3%) while atrial enlargement was present in 548 patients (64.2%). Atrial enlargement as mild in 145 patients (16.9%), moderate in 203 patients (23.8%) and severe in 197 (23.1%).

Within 90 days, 63 patients (7.4%) of those who underwent TTE had at least a study outcome event: 49 recurrent ischemic stroke, 8 TIA and 6 symptomatic systemic embolism. Three patients had two study outcome events. The TTE characteristics of the patients with and without outcome event are summarized in table 3. Atrial enlargement was present in 81% of the patients with recurrent ischemic events. The risk of outcome event increased with the severity of atrial enlargement (p for trend: 0.012) (Fig.1). The recurrence rate in the 197 patients with severe left atrial enlargement was 11.7%.

Therapy with anticoagulants after the index stroke event was performed in 80.5% of the patients without atrial enlargement, in 79.3% with mild atrial enlargement, in 77.6% with moderate atrial enlargement and in 77.1% of the patients with severe atrial enlargement (p for trend: 0.78).

On multivariate analysis, the presence of atrial enlargement (OR=2.13; 95% CI 1.06-4.29, p=0.033) and CHA_2DS_2-VASc score (OR 1.22; 95% CI 1.04-1.45, p=0.018, for each point increase) were correlated with ischemic recurrent event. Small ischemic lesion was inversely correlated with ischemic recurrent event (OR 0.55; 95% CI 0.30-1.00, p=0.05). The presence of pacemaker showed an OR 2.10; 95% CI 0.97-4.60, p=0.06. When in the model the variable atrial enlargement was introduced as mild, moderate or severe, only the presence of severe atrial enlargement was correlated with an outcome event (OR: 2.05; 95% CI 1.08-2.87, p=0.027). All the remaining TTE characteristics were not correlated with outcome event.

Figure 2 shows the adjusted analysis using the Cox regression model that evidences the different risk for an ischemic outcome event according to the severity of atrial

enlargement within 90 days. This analysis, was adjusted for age, sex, CHA2DS2-VASc score, lesion size, anticoagulant therapy and NIHSS score on admission.

Discussion

In this prospective study in patients with acute stroke and AF, TTE showed a left atrial thrombus in about 1% and an atrial enlargement in 65% of the patients. The presence of atrial enlargement was associated with a higher risk of an ischemic recurrence within 90 days. This association was accounted for by severe atrial enlargement.

In clinical practice, for the fear of an early recurrence, TTE is usually performed in acute phase of stroke to detect a thrombus and to start anticoagulant therapy earlier. This study showed the futility of acute TTE for detection of intra-cardiac thrombosis. About 17% of the patients did not undergo TTE in the acute phase of stroke and these patients were older and with more severe neurological deficit. Therefore, it is possible that in these patients, the rate of intra-cardiac thrombus was higher. However, these are not the typical patients in whom anticoagulation would be started promptly.

Several studies demonstrated that TEE is superior to TTE for identification of a cardiac embolic source in patients with TIA or stroke (11,12). De Brujn et al. (11), in patients with acute stroke, found a thrombus in 17% of the patients using TEE compared to 2% using TTE. Thus, in patients with acute stroke and AF, TEE is probably more useful to detect intra-cardiac thrombosis. However, this examination in patients with acute stroke is not easy.

Our study showed that atrial enlargement, especially severe, was independently associated with early stroke recurrence. Several studies found that moderate to severe left atrial enlargement is an independent marker of recurrent stroke of embolic subtypes in patients with ischemic stroke even in patients without evidence of AF (3,13). Furthermore, atrial dilatation is correlated with more severe stroke (14).

An association between ischemic recurrent events and the presence of a valve prosthesis, biological or mechanical, was not found but the number of patients with valve prosthesis was low (17 patients with biological prosthesis and 40 with mechanical prosthesis).

This study has several limitations and strengths. The evaluation of TTE and the adjudication of the outcome events were not centralized. Not all the patients had TTE examination and this might have introduced some selection bias.

Strengths of our study include the prospective and multicentre design with an adequate sample size of consecutive patients, making the results robust and generalizable. Furthermore, we collected data on a wide range of potentially confounding risk factors, allowing us to estimate the independent effects of TTE characteristics evaluated.

In summary, in patients with AF-associated acute stroke, atrial enlargement is an independent marker of recurrent stroke and systemic embolism. Left atrial thrombosis is relatively uncommon. Future studies are needed to evaluate whether left atrial enlargement could be used to drive prompt anticoagulant therapy in patients with acute stroke and AF to reduce the risk of recurrence.

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Figure legends

Figure 1. The risk of an ischemic outcome event according to the severity of atrial enlargement (p for trend: 0.012).

Figure 2. The cumulative risk of an ischemic outcome event according to the severity of atrial enlargement using Cox regression model.

Table1. Definitions of left atrial enlargement according to the severity (Lang et al, 2005)

	Women				Men			
	Reference Range	**Mildly abnormal**	**Moderately abnormal**	**Severely abnormal**	**Reference Range**	**Mildly abnormal**	**Moderately abnormal**	**Severely abnormal**
Atrial dimension								
LA diameter, cm	2.7-3.8	3.9-4.2	4.3-4.6	≥4.7	3.0-4.0	4.1-4.6	4.7-5.2	≥5.2
LA diameter/BSA,cm/m^2	1.5-2.3	2.4-2.6	2.7-2.9	≥3.0	1.5-2.3	2.4-2.6	2.7-2.9	≥3.0
Atrial area								
LA area, cm^2	≤20	20-30	30-40	>40	≤20	20-30	30-40	>40
Atrial volumes								
LA volume, mL	22-52	53-62	63-72	≥73	18-58	59-68	69-78	≥79
LA volume/BSA,mL/m^2	22±6	29-33	34-39	≥40	22±6	29-33	34-39	≥40

LA: left atrial

BSA: body surface area in m^2

Table 2. Characteristics of the patients with or without TTE evaluation.

	Total (n=1029)	**With TTE (n=854)**	**Without TTE (n=175)**	**p**
Age (mean, years)	77.2 ± 9.5	76.3 ± 9.5	81.4 ± 8.4	0.0001
NHISS (mean)	9.2 ±7.3	8.9 ± 7.0	10.7 ± 9.0	0.002
Sex male	468 (45.5%)	398 (46.6%)	70 (40.0%)	0.1
Diabetes mellitus	264 (25.6%)	221 (26.0%)	43 (24.8%)	0.7
Statins	260 (25.3%)	213 (25.2%)	47 (27.3%)	0.5
Hipertension	821 (79.8%)	676 (79.8%)	145 (83.8%)	0.2
Hyperlipidemia	332 (32.3%)	282 (33.4%)	50 (29.2%)	0.3
History stroke/TIA*	266 (25.8%)	205 (24.3%)	61 (35.5%)	0.04
Smoking	190 (18.5%)	158 (18.7%)	32 (18.5%)	0.5
Alcoholism	68 (6.6%)	57 (6.7%)	11 (6.4%)	1.0
History of CHF**	193 (18.7%)	167 (19.6%)	26 (15.0%)	0.2
History of MI***	166 (16.1%)	142 (16.8)	24 (13.9%)	0.4
Paroxysmal AF	364 (35.4%)	316 (37.0%)	48 (27.9%)	0.023
Permanent AF	473 (46.0%)	385 (45.1%)	88 (51.2%)	0.1
Persistent AF	191 (18.6%)	155 (18.2%)	36 (20.9%)	0,3
Pacemaker	85 (8.3%)	70 (8.2%)	15 (8.7%)	0.8
rtPA	184 (17.9%)	158 (18.5%)	26 (15.1%)	0.3
Intra-arterial revascularization	46 (4.5%)	43 (5.1%)	3 (1.7%)	0.067
CHA_2DS_2-VASc 0	17 (1.6%)	16 (1.9%)	1 (0.6%)	0.053
1	54 (5.2%)	51 (6.0%)	3 (1.7%)	
2	91 (8.8%)	82 (9.6%)	9 (5.1%)	
3	200 (19.4%)	167 (19.5%)	33 (18.9%)	
4	243 (23.6%)	203 (23.8%)	40 (22.9%)	
5	206 (20.0%)	161 (18.8%)	45 (25.7%)	
6	129 (12.5%)	104 (12.2%)	25 (14.3%)	
7	66 (6.4%)	51 (6.0%)	15 (8.6%)	
8-9	23 (2.2)	19 (2.2%)	4 (2.3%)	
Therapy with anticoagulants after index stroke	766 (74.4%)	673 (78.8%)	93 (53.1%)	0.0001
Recurrent ischemic event****	77 (7.6%)	63 (7.4%)	14 (8.0%)	0.7
Disability at 90 days (mRS≥3)	510 (49.5%)	403 (47.6%)	107 (61.8%)	0.001

*Transient Ischemic attack

**Congestive heart failure

***Myocardial infarction

****Stroke/TIA/systemic embolism

Table 3. TTE characteristics in patients with and without outcome event

	Total (n=854)	**Without outcome event (n =791)**	**With outcome event (n= 63)**	**p**
Atrial enlargement	548 (64.2%)	497 (62.8%)	51 (81.0%)	0.004
Mild	145 (16.9%)	133 (16.9%)	12 (19.0%)	0.6
Moderate	203 (23.8%)	187 (23.7%)	16 (25.4)	0.7
Severe	197 (23.1%)	174 (22.0%)	23 (36.5%)	0.013
Intracardiac thrombus	11 (1.3%)	10 (1.3%)	1 (1.6%)	0.5
Cardiomyopathy*	99 (11.6%)	89 (11.3%)	10 (15.9)	0.3
Mitral disease	360 (42.2%)	323 (40.1%)	37 (58.7%)	0.021
Aortic disease	230 (26.9%)	205 (25.9%)	25 (39.7%)	0.026
Tricuspidal disease	213 (24.9%)	189 (23.9%)	24 (38.1%)	0.016
Biological aortic valve	10 (1.2%)	10 (1.2%)	0	1.0
Mechanical aortic valve	17 (2.0%)	15 (1.8%)	2 (3.0%)	0.3
Biological mitral valve	7 (0.8%)	7 (0.8%)	0	1.0
Mechanical mitral valve	23 (2.7%)	20 (2.4%)	3 (4.5%)	0.2

*left ventricular ejection ≤40%

Figure 1

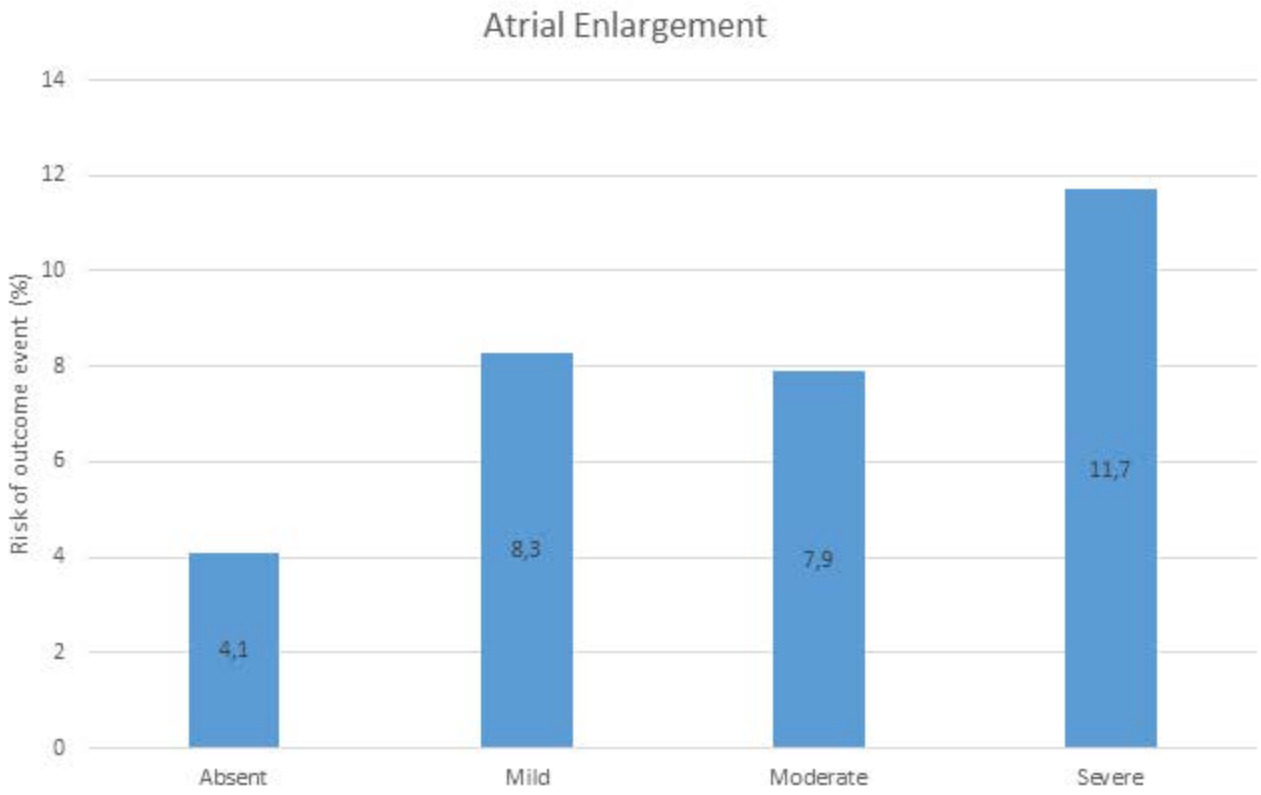
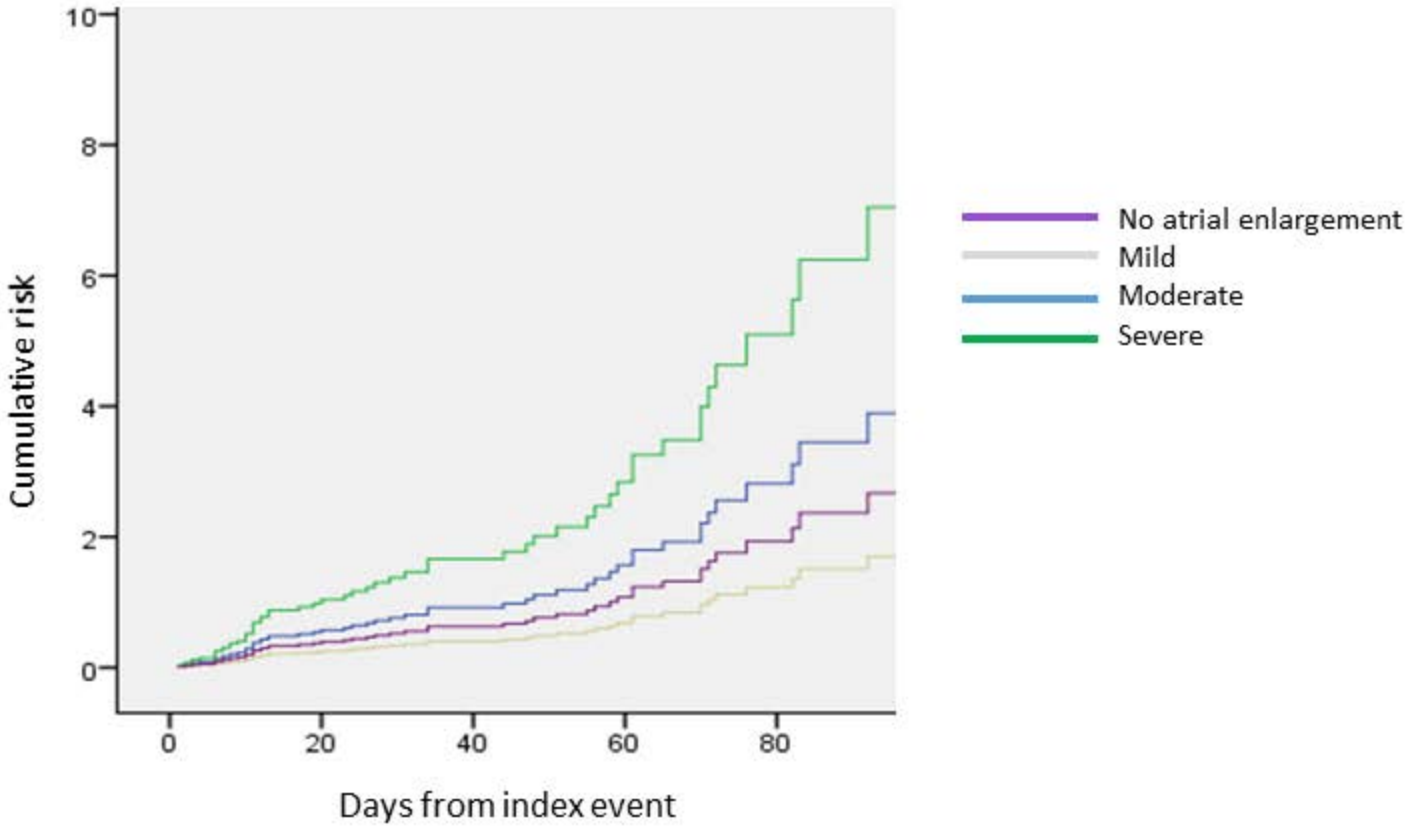

Atrial Enlargement
Risk of outcome event (%)
14
12
10
8
6
4
2
0
4,1
8,3
7,9
11,7
Absent
Mild
Moderate
Severe

Figure 2



Reference: no atrial enlargement
Mild atrial enlargement: HR 0.64 (95% CI 0.28-1.40), p=0.3
Moderate atrial enlargement: HR 1.47 (95% CI 0.54-4.00), p=0.4
Severe atrial enlargment: HR 2.64 (95% CI 1.00-6.97), p=0.049