Effect of Mitral Regurgitation on Thrombotic Risk in Patients With Nonrheumatic Atrial Fibrillation: A New CHA_2DS_2-VASc Score Risk Modifier?

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The current study assessed the effect of mitral regurgitation (MR) on thrombotic risk in nonrheumatic atrial fibrillation (AF). AF carries a thrombotic risk related to left atrial blood stasis. The prevalence of atrial thrombosis, defined as the presence of left atrial appendage thrombus and/or left atrial spontaneous echo contrast grade >2, was determined in 686 consecutive nonrheumatic AF patients without (adequate) anticoagulation scheduled for transesophageal echocardiography before electrical cardioversion and was related to the severity of MR adjusted for the CHA_2DS_2-VASc score. A total of 103 (15%) patients had severe MR, 210 (31%) had moderate MR, and 373 (54%) had no-mild MR; the median CHA_2DS_2-VASc score was 3.0 (interquartile range 2.0 to 4.0). Atrial thrombosis was observed in 118 patients (17%). The prevalence of atrial thrombosis decreased with increasing MR severity: 19.9% versus 15.2% versus 11.6% for no-mild, moderate, and severe MR, respectively (p value for trend = 0.03). Patients with moderate and severe MR had a lower risk of atrial thrombosis than patients with no-mild MR, with adjusted odds ratios of 0.51 (95% confidence interval 0.31 to 0.84) and 0.24 (95% confidence interval 0.11 to 0.49), respectively. The protective effect of MR was present across all levels of the CHA_2DS_2-VASc risk score and the presence of moderate-severe MR in patients with an intermediate CHA_2DS_2-VASc score (2 to 3) lowered the atrial thrombotic risk to the level of patients with a low CHA_2DS_2-VASc score (0 to 1). In conclusion, our data show that the presence of MR attenuated the atrial thrombotic risk by more than 50% in patients with nonrheumatic AF. **(Am J Cardiol 2021;145:69−76)**

Atrial fibrillation (AF) significantly increases the risk of ischemic stroke (IS), but the risk varies strongly depending on the individual patient's stroke risk factors.[1] Many scores, such as the CHA_2DS_2-VASc score, have been developed to guide physicians in their decision to start anticoagulation.[2] However, the risk prediction with these models is modest at best (C-statistic = 0.6).[3,4] Severe mitral regurgitation (MR) has been shown to decrease left atrial (LA) thrombus formation and systemic thromboembolic (TE) events in AF patients with rheumatic valve disease with an observed risk reduction of more than 50%.[5−8] In nonrheumatic AF, however, direct evidence of a lower incidence of thrombus or left atrial spontaneous echo contrast (LASEC) in patients with MR is still controversial. Therefore, the present observational study was designed to assess the incremental value of MR presence to predict thrombotic risk on top of the CHA_2DS_2-VASc score in a consecutively enrolled nonrheumatic AF population scheduled for transesophageal echocardiography (TEE) before synchronized electrical cardioversion.

Methods

The target study population consisted of 795 consecutive patients who were referred for electrical cardioversion for AF at our tertiary referral center from January 2013 until December 2018 and who underwent a TEE before cardioversion to exclude left atrial appendage thrombus (LAAT) or severe LASEC. In our center, TEE before AF cardioversion is performed in all patients without evidence of adequate anticoagulation during at least 3 weeks before cardioversion, including patients in whom medication compliance was judged problematic. A total of 109 patients were excluded because of associated mitral valve stenosis (n = 10), status postmitral valve surgery (n = 11), status post left atrial appendage (LAA) ligation/LAA closure device (n = 31), active oncological disease (n = 49), or missing data/poor echo visualization (n = 8). The final study population consisted of 686 AF patients.

Classification of AF as paroxysmal or persistent according to the criteria of the European Society of Cardiology guidelines was achieved in 544 patients.[9] Clinical information was collected based on chart review, including demographic data, cardiac risk factors (hypertension, diabetes mellitus, dyslipidemia), and comorbid medical conditions that allowed the calculation of the CHA_2DS_2-VASc score. CHA_2DS_2-VASc scores of 0 to 1, 2 to 3, and >3 were classified as low, intermediate, and high risk, respectively. The

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study was approved by the ethics committee of the Antwerp University Hospital.

All echocardiographic examinations were carried out by trained sonographers using high-quality cardiovascular ultrasound systems. MR severity was graded on TEE images according to the American Society of Echocardiography guidelines based on a validated multi-integrative method.[10] Both qualitative (color flow mapping) and quantitative measurements (proximal isovelocity surface area whenever feasible) were used to grade the MR severity as no-mild, moderate, or severe. Left ventricular ejection fraction (LVEF) was assessed semi-quantitatively as good (LVEF >55%), moderate (LVEF = 40% to 55%) or poor (LVEF <40%) based upon either left ventricular (LV) volume measurements or visual estimation.

LA volumes adjusted for body surface area were measured and calculated offline on a transthoracic echocardiography close to the timing of the TEE by one expert using the area-length method.

Patients were evaluated for the presence of LAAT and LASEC with TEE using appropriate gain settings for optimal visualization (see example in Figure 1). LAAT was identified as independently mobile round, oval, or irregularly shaped echodensities. LASEC was defined as a pattern of slowly swirling intracavitary echodensities imaged with gain settings adjusted to distinguish background noise. LASEC was assessed semi-quantitatively as proposed by Fatkin et al, who demonstrated an excellent correlation between visual grading of LASEC (grades 0 to 4+) and video-densitometry analysis.[11] LASEC gradation of all TEE images was performed offline by one expert.

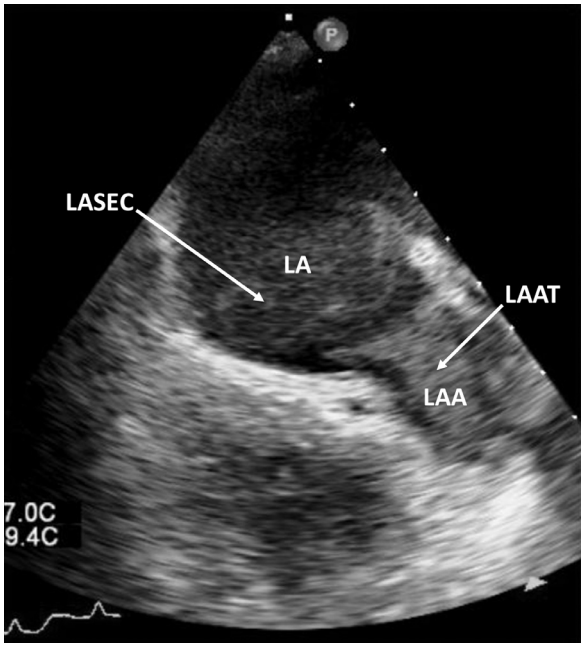

Figure 1. A transesophageal echocardiographic image of the left atrium and left atrial appendage showing left atrial spontaneous echo contrast grade 4 and a left atrial appendage thrombus in a patient with no-mild mitral regurgitation. LA = left atrium; LAA = left atrial appendage; LAAT = left atrial appendage thrombus; LASEC = left atrial spontaneous echo contrast.

The thrombotic endpoint was atrial thrombosis defined as the presence of LAAT and/or LASEC >2 on TEE. Previous studies have demonstrated that these atrial thrombotic parameters strongly predict the occurrence of clinical TE events and that they can be used as valid surrogate endpoints of thrombotic risk.[12–14]

Sample size was calculated based upon an estimated 15% prevalence of LAAT/LASEC >2 in patients with no-mild MR and a 7.5% prevalence in patients with moderate-severe MR (50% risk reduction). With a type 1 error of 0.05, a type 2 error of 0.20, and an expected no-mild/moderate-severe MR ratio of 2/1, a sample size of 638 patients was calculated. Assuming an exclusion rate of 15%, we needed to enroll at least 750 patients.

Categorical variables are labeled as number of patients (percentage), and continuous variables are described as the mean ± standard deviation (SD) or as median values with interquartile range. Between-group comparisons were made with the chi-square test for categorical variables and with ANOVA (1-way ANOVA or Kruskal-Wallis test for non-parametric testing) for continuous variables. Independent predictors of atrial thrombosis were assessed by stepwise logistic regression analysis. The following factors were included in the model: CHA_2DS_2-VASc score, LV function (poor vs moderate-good), left atrial volume index (LAVI) (small vs large), and MR grade. For discrimination between small and large atria, a LAVI cutoff value of 37 ml/m^2 was determined based upon receiving operating characteristic analysis. A sensitivity analysis was performed to assess the predictive value of MR in prespecified subgroups (small vs large LA, poor vs good LV function, low vs intermediate vs high CHA_2DS_2-VASc score risk groups, and no anticoagulation vs inadequate anticoagulation). A 2-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

The study population consisted of 686 AF patients (72% male) with a mean age of 67 ± 11 years. All patients underwent TEE before cardioversion either because of lack of anticoagulation (46%) or because of inadequate anticoagulation with either standard oral anticoagulation (OAC, 25%) or direct oral anticoagulation (DOAC, 29%). All patients were divided into 3 levels of the CHA_2DS_2-VASc risk score; 23% were low risk (0 to 1), 40% were intermediate risk (2 to 3), and 37% were high risk (>3). Table 1 describes the clinical characteristics of patients in the different MR categories. The severe MR group contained more female patients. The patients in this group were older, had more chronic kidney disease and congestive heart failure, and had a higher CHA_2DS_2-VASc score.

TEE revealed atrial thrombosis (LAAT and/or LASEC >2) in 118 patients (17%). LAAT was observed in 58 patients of which 46 also showed LASEC >2. LASEC >2 without LAAT was observed in 60 patients. The presence of atrial thrombosis was observed in 10.6% of patients with a low CHA_2DS_2-VASc score, 15.0% of patients with an intermediate CHA_2DS_2-VASc score, and 23.9% of patients with a high CHA_2DS_2-VASc score (p value = 0.001). The

Table 1
Clinical characteristics of patients in the different mitral regurgitation categories

Characteristics	Mitral regurgitation			p value
	No-mild (n = 373)	Moderate (n = 210)	Severe (n = 103)	
Age (years)	65.1 ± 11.1	69.7 ± 10.6	70.0 ± 11.2	<0.001
Female	76 (20.4%)	73 (34.8%)	41 (39.8%)	<0.0001
BMI (kg/m^2)	28.2 ± 4.9	27.9 ± 5.5	27.4 ± 4.9	0.346
Systolic blood pressure (mm Hg)	133.3 ± 23.3	133.9 ± 22.1	131.6 ± 22.4	0.704
Diastolic blood pressure (mm Hg)	83.3 ± 15.7	82.4 ± 15.5	83.3 ± 14.9	0.777
Paroxysmal/persistent AF	160/142 (53.0%/47.0%)	103/63 (62.0%/38.0%)	43/33 (56.6%/43.4%)	0.17
Chronic kidney disease	56 (15.0%)	59 (28.1%)	30 (29.1%)	0.0001
eGFR (ml/min/1.73 m^2)	73.9 ± 20.1	68.1 ± 21.4	63.8 ± 22.1	<0.001
Congestive heart failure	72 (19.3%)	64 (30.5%)	45 (43.7%)	<0.0001
Hypertension	226 (60.6%)	138 (65.7%)	59 (57.3%)	0.29
Diabetes mellitus	74 (19.8%)	49 (23.3%)	22 (21.4%)	0.61
History of stroke, TIA or TE	57 (15.3%)	26 (12.4%)	12 (11.7%)	0.49
Vascular disease	147 (39.4%)	85 (40.5%)	51 (49.5%)	0.17
Hypercholesterolemia	224 (60.1%)	121 (57.6%)	52 (50.5%)	0.22
Medication				
Antiplatelet agent	134 (35.9%)	79 (37.6%)	40 (38.8%)	0.83
Antiarrhythmics	96 (25.7%)	60 (28.6%)	27 (26.2%)	0.75
No anticoagulation	174 (46.6%)	88 (41.9%)	53 (51.5%)	0.26
Echocardiographic findings				
LVEF (%)	53.4 ± 14.1	50.7 ± 15.5	44.9 ± 15.1	<0.001
LAVI (ml/m^2)	36.6 ± 11.3	41.0 ± 13.2	49.3 ± 16.5	<0.001
CHA_2DS_2-VASc score				
Total CHA_2DS_2-VASc score	3.0 (1.0-4.0)	3.0 (2.0-5.0)	3.0 (2.0-5.0)	<0.001

AF = atrial fibrillation; BMI = body mass index; eGFR = estimated glomerular filtration rate; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; TE = thromboembolism; TIA = transient ischemic attack.

Categorical data are presented as n (%). Continuous data are presented as mean ± standard deviation (SD), or median (interquartile range [IQR]) according to the distribution.

increase in atrial thrombosis with increasing CHA_2DS_2-VASc score was mainly driven by increasing LASEC >2 prevalence (Figure 2). Atrial thrombosis was found in 4 of 69 (6%) patients with a CHA_2DS_2-VASc score of 0 and in 13 of 91 (14.3%) patients with a CHA_2DS_2-VASc score of 1.

Figure 3 shows the presence of atrial thrombosis according to MR severity and describes the independent predictors of atrial thrombosis. Atrial thrombosis decreased with increasing MR severity: 19.9% versus 15.2% versus 11.6% for patients with no-mild, moderate, and severe MR, respectively (p value for trend = 0.03). The decrease in atrial thrombosis was mainly driven by decreasing LASEC >2 prevalence. In addition to the CHA_2DS_2-VASc score, poor LVEF, and large LAVI, MR was also independently associated with atrial thrombosis. Table 2 shows the unadjusted and adjusted odds ratios (ORs) with 95% confidence interval (CI) of the independent predictors of atrial thrombosis. Patients with moderate and severe MR had a lower risk of atrial thrombosis than those with no-mild MR, with adjusted ORs of 0.51 (95% CI 0.31 to 0.84) for moderate MR and 0.24 (95% CI 0.11 to 0.49) for severe MR. The C-statistic of the regression model increased significantly (p value = 0.0003) from 0.62 to 0.75 by adding MR grade, LV function, and LAVI to the univariate CHA_2DS_2-VASc score model.

Additional analysis revealed that the protective effect of MR was present across all levels of the CHA_2DS_2-VASc risk score and was independent of LA size, LV function, and inadequate/no anticoagulation treatment (for more details, see Table 3). Figure 4 shows the observed differences in atrial thrombosis for the different CHA_2DS_2-VASc score risk groups. Patients in the intermediate CHA_2DS_2-VASc score risk group but with a significant MR had a documented atrial thrombotic risk of 10.7% (13/122 patients), which was as low as in the "low risk" group. On the other hand, patients in the low CHA_2DS_2-VASc score risk group but with LAVI >37 ml/m^2 and without significant MR had a documented high atrial thrombotic risk of 26% (9/35 patients). The latter is not shown in this figure.

Discussion

AF is a nonbenign disease with a substantial risk of TE events such as IS or systemic embolism. The TE risk is closely related to the presence of LASEC and/or LAAT. In addition to LAA dysfunction, altered coagulation factors, such as D-dimers and von Willebrand factor, and a low shear stress (predominantly present in large atria), contribute to the formation of LASEC and LAAT.[15,16]

The present study shows that the presence of moderate-severe MR was associated with a more than 50% reduction in the risk of atrial thrombosis in AF patients, independent of the CHA_2DS_2-VASc risk score.

The underlying mechanistic concept is that MR produces turbulent flow into the LA cavity, thereby preventing red blood cells from aggregating, with subsequent attenuation of LASEC and LAAT formation (a wash-out effect). In

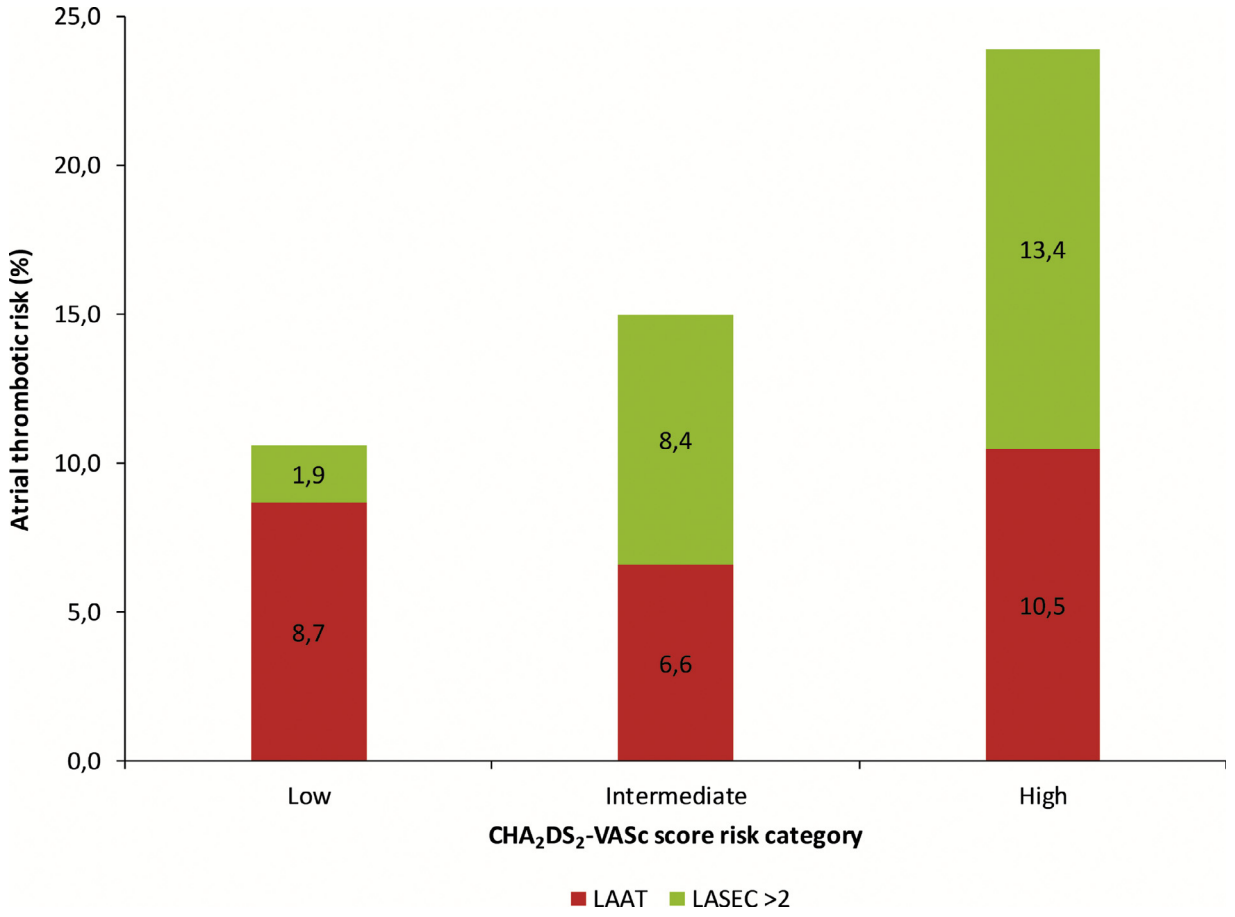

Figure 2. Bar graph showing the prevalence of atrial thrombosis (left atrial appendage thrombus or left atrial spontaneous echo contrast >2) in patients with low (0 to 1), intermediate (2 to 3), and high (>3) CHA_2DS_2-VASc score. p value = 0.001. LAAT = left atrial appendage thrombus; LASEC = left atrial spontaneous echo contrast.

addition, less coagulation activity (eg, less thrombin-antithrombin III complex) and lower D-dimer levels have been observed in patients with nonrheumatic AF and a higher degree of MR.[17,18] The presence of severe MR seems to prevent LA stasis and is therefore the first documented "protective" factor of thrombotic risk in patients with nonrheumatic AF. Our observation that MR predominantly affects LASEC formation and not LAAT formation might be related to the fact that MR jets often do not reach the LAA. In the recent and large study by Cresti et al, the incidence of LA thrombus formation was also the same in the group of patients without MR compared with the group with severe MR.[19] Our findings concur with previous work showing a reduced risk for atrial thrombosis or cardioembolic events in nonrheumatic AF patients with severe MR.[19–23] In all these studies, however, no appropriate correction was made for the CHA_2DS_2-VASc risk score; therefore, the exact adjusted ORs could not be provided. Inappropriate correction for clinical thrombotic risk factors and/or small study populations are probably the reasons why some other older studies did not find a link between MR and thrombotic risk.[24,25] The more recent study by Bisson et al, which included a large unselected population of AF patients, showed a nonsignificant small protective effect (OR = 0.88) of severe MR for IS/TE events after adjustment for the CHA_2DS_2-VASc risk score.[26] However, the majority of these patients were under anticoagulant treatment, which might have attenuated the protective effect of severe MR. In the present study design with TEE evaluation before cardioversion to exclude atrial thrombosis, patients did not receive anticoagulation or were inadequately anticoagulated. The observed increased rate of atrial thrombosis with increasing CHA_2DS_2-VASc risk score parallels the increased risk of IS/TE events with increasing CHA_2DS_2-VASc risk score documented in previous risk score validation studies.[3] This underscores the reliable relationship between atrial thrombosis and future cardioembolic events. Nevertheless, the present study highlights that adding echocardiographic parameters such as MR, LAVI, and LVEF significantly increases the predictive risk model compared with clinical risk factors imbedded in the CHA_2DS_2-VASc risk score. Therefore, these factors may be clinically relevant risk modifiers. More specifically, in nonrheumatic AF patients with a low to intermediate CHA_2DS_2-VASc risk score, the presence of significant MR could allow to downsize the dosage of antithrombotic treatment, particularly if the patient also has an increased bleeding risk. On the other hand, in

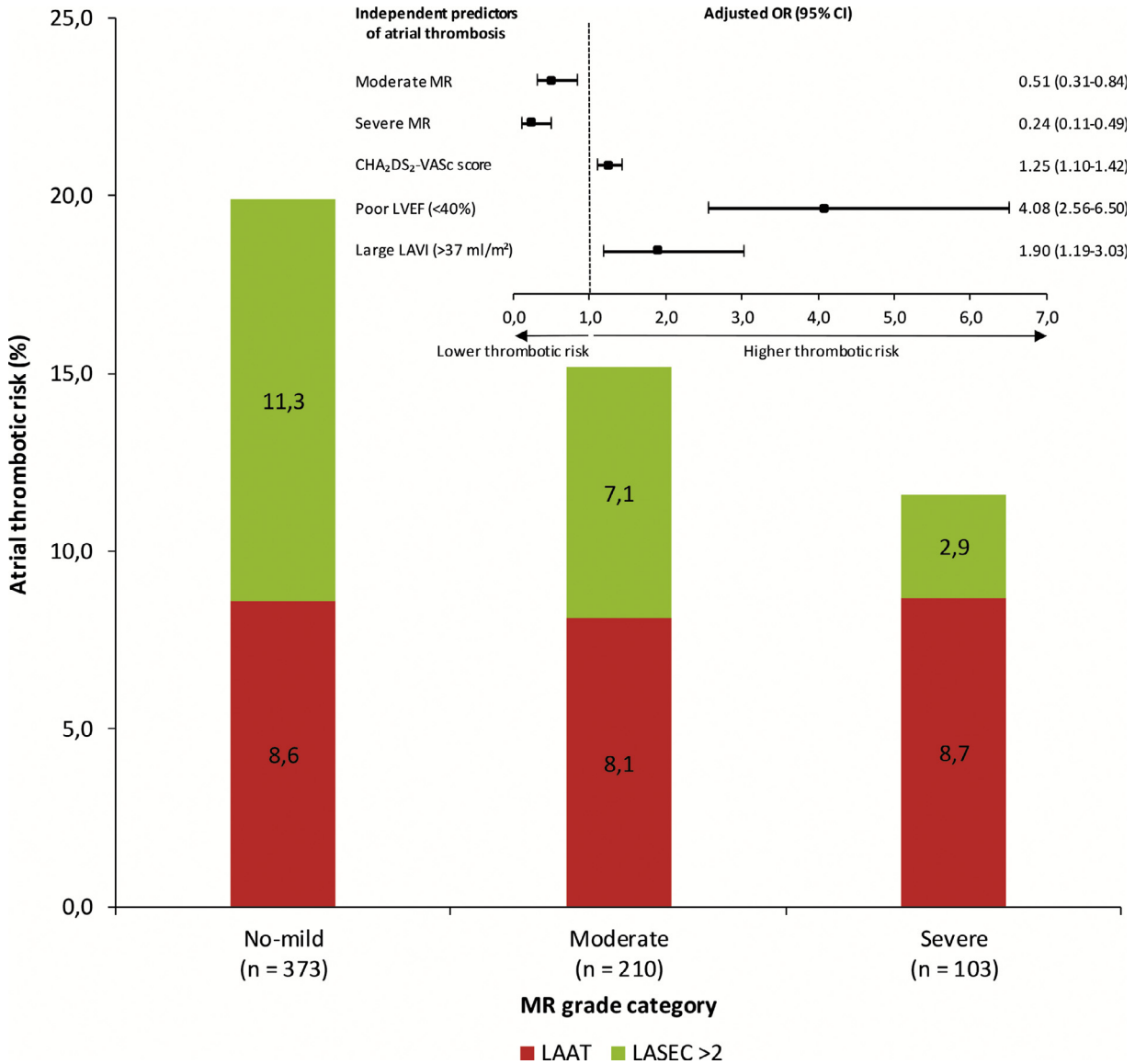

Figure 3. Bar graph showing the prevalence of atrial thrombosis (left atrial appendage thrombus or left atrial spontaneous echo contrast >2) in patients with no-mild, moderate, and severe mitral regurgitation. p value for trend = 0.03. In the upper right corner, the adjusted odds ratio and 95% confidence interval is shown for each independent predictor of atrial thrombosis. CI = confidence interval; LAAT = left atrial appendage thrombus; LASEC = left atrial spontaneous echo contrast; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; OR = odds ratio.

patients with low CHA_2DS_2-VASc risk scores, the presence of a large LAVI in the absence of a significant MR could lower the threshold to start anticoagulation therapy.

Table 2
Independent predictors of atrial thrombosis

Predictors	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
CHA_2DS_2-VASc score	1.28 (1.14-1.44)	1.25 (1.10-1.42)
Moderate MR vs no-mild MR	0.73 (0.47-1.16)	0.51 (0.31-0.84)
Severe MR vs no-mild MR	0.53 (0.28-1.02)	0.24 (0.11-0.49)
Poor LVEF (<40%)	4.26 (2.78-6.52)	4.08 (2.56-6.50)
Large LAVI (>37 ml/m^2)	1.97 (1.29-3.03)	1.90 (1.19-3.03)

CI = confidence interval; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; OR = odds ratio.

The results of this study should be considered in light of the following limitations. The retrospective study design and the medium-sized study population did not allow us to assess the effect of MR on future cardioembolic events. However, as thrombotic risk has been reduced dramatically thanks to adequate anticoagulation strategies, it will be hard to investigate a thrombotic risk factor based upon clinical endpoints in the current clinical practice of AF patients. The evaluation of atrial thrombosis before cardioversion might therefore be a valid surrogate marker of cardioembolic events. In this study, only patients with nonpermanent AF were included, so the exact effect of MR on atrial thrombosis in patients with permanent AF could not be derived. However, as permanent AF is mainly characterized by larger atria and as the protective effect of MR was independent of atrial size, similar protective effects of MR can

Table 3
Adjusted odds ratio for moderate-severe mitral regurgitation versus no-mild mitral regurgitation for different subgroups

Predictors	Adjusted OR Moderate-severe MR versus no-mild MR	95% lower CI	95% upper CI	p value*
CHA_2DS_2-VASc score				0.35
Low	0.88	0.30	2.61	
Intermediate	0.39	0.18	0.83	
High	0.36	0.19	0.69	
LA dimension				0.39
LAVI ≤37 ml/m^2	0.55	0.25	1.22	
LAVI >37 ml/m^2	0.36	0.20	0.63	
LV function				0.83
LVEF <40%	0.44	0.21	0.90	
LVEF ≥40%	0.39	0.22	0.71	
Anticoagulation				0.16
No	0.62	0.30	1.28	
Yes (inadequate dose)	0.32	0.18	0.58	

CI = confidence interval; LA = left atrium; LAVI = left atrial volume index; LV = left ventricle; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; OR = odds ratio.
* p value for interaction.

be expected in permanent AF. Finally, we were not able to assess the effect of MR chronicity on LA thrombus formation. However, the reported observation that LASEC and suspicious thrombus formation may occur immediately after successful MR reduction with the MitraClip system, may mitigate the importance of MR duration on the process of LA thrombus formation.[27]

In conclusion, the presence of MR attenuates thrombotic risk in patients with nonrheumatic AF. If these findings could be confirmed in an unselected AF population, this

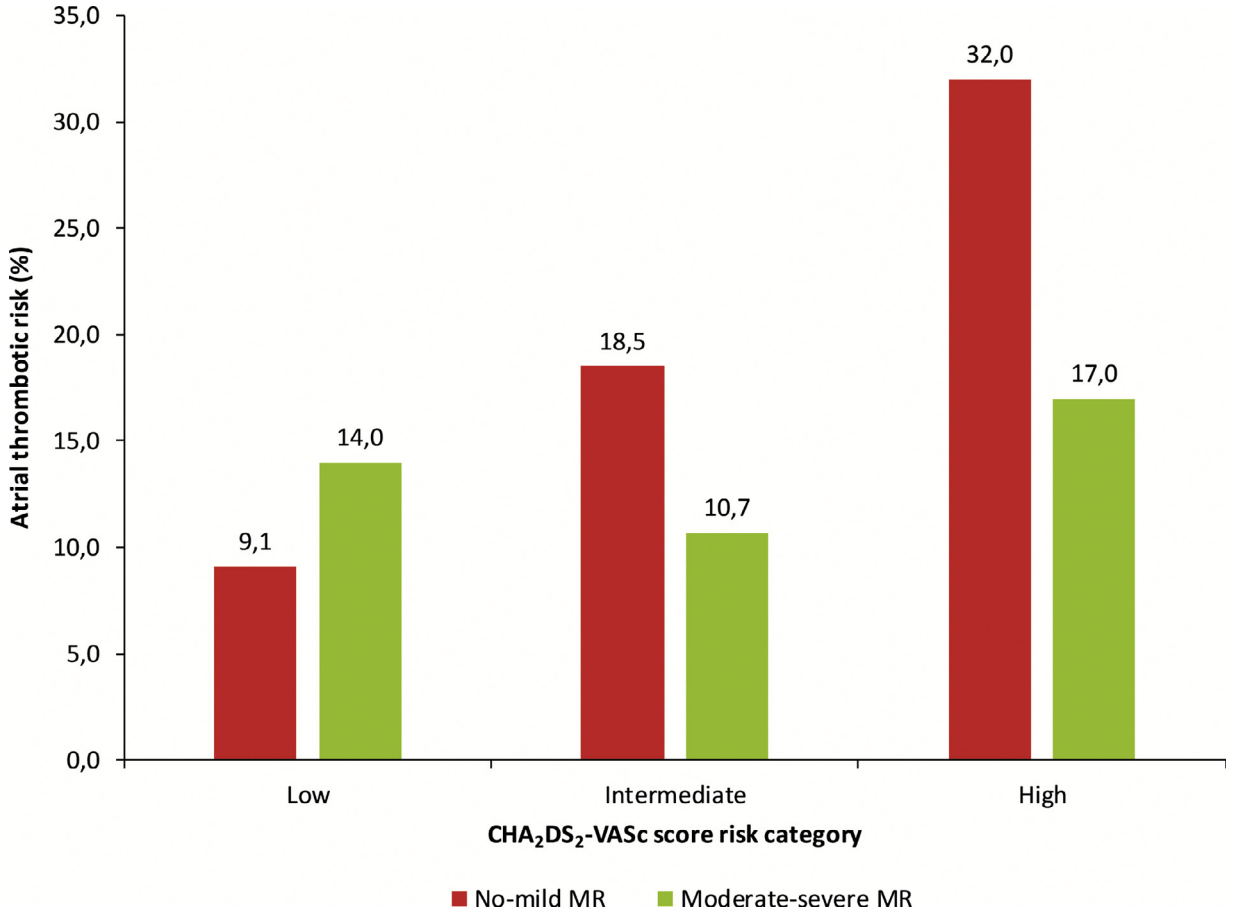

Figure 4. Bar graph showing the prevalence of atrial thrombosis (left atrial appendage thrombus and/or left atrial spontaneous echo contrast >2) in patients with low (0 to 1), intermediate (2 to 3), and high (>3) CHA_2DS_2-VASc score stratified by no-mild and moderate-severe mitral regurgitation. LAAT = left atrial appendage thrombus; LASEC = left atrial spontaneous echo contrast; MR = mitral regurgitation.

parameter might be considered a new risk modifier of the CHA_2DS_2-VASc score and might help refine the indication and dosage of anticoagulants in AF patients.

Author Contribution

Sven L. Van Laer: Conceptualization; Data curation; Formal analysis; Software; Visualization; Writing - original draft; Writing - review & editing.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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