ORIGINAL ARTICLE

Serum galectin-3 level predicts early recurrence following successful direct-current cardioversion in persistent atrial fibrillation patients

Persistan atriyal fibrilasyonlu hastalarda serum galektin-3 seviyeleri başarılı elektriksel kardiyoversiyondan sonra erken nüksü öngördürür

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ABSTRACT

Objective: Atrial structural remodeling has been suggested to contribute to atrial fibrillation (AF) recurrence following direct-current cardioversion (DCCV). The role of several inflammatory and extracellular matrix turnover markers in AF recurrence following DCCV has been investigated. However, data on the impact of galectin-3, which is known to play a role in various fibrotic conditions, including cardiac fibrosis are lacking. The aim of this study was to demonstrate the predictive role of serum galectin-3 levels in AF recurrence following successful DCCV.

Methods: A total of 90 persistent AF patients who were scheduled for DCCV were prospectively enrolled. Serum samples were assayed to determine pre-DCCV galectin-3 levels using the enzyme-linked immunosorbent assay method. Patients were followed up for 3 months for AF recurrence.

Results: Of 90 persistent AF patients (mean age: 55.33±7.94 years; 53.33% male) who underwent successful DCCV, 28 (31.11%) experienced early AF recurrence within 3 months. Patients with AF recurrence had a greater left atrial volume index (LAVI) (33.35± 2.45 mL/m^2 vs. 29.21±3.08 mL/m^2; p<0.001) and serum galectin-3 levels were higher (0.88 ng/mL [min-max: 0.52–1.32] vs. 0.60 ng/mL [min-max: 0.38–0.91]; p<0.001). In multivariate analysis, the number of DCCV attempts (hazard ratio [HR]: 1.879, 95% confidence interval [CI]: 1.052–3.355; p=0.033), LAVI (HR: 1.180, 95% CI: 1.028–1.354; p=0.018), and serum galectin-3 level (HR: 11.933, 95% CI: 1.220–116.701; p=0.033) were found to be independently associated with early AF recurrence following successful DCCV.

Conclusion: Circulating levels of galectin-3 may have an association with early AF recurrence following DCCV.

ÖZET

Amaç: Atriyal yeniden şekillenmenin elektriksel kardiyoversiyondan sonra atriyal fibrilasyon (AF) nüksünde katkısı bulunduğu düşünülmektedir. Daha önceki çalışmalarda, enflamasyon ve ektraselüler matriks döngüsü ile ilişkili belirteçlerin elektriksel kardiyoversiyon sonrası AF nüksü ile ilişkisi incelenmiştir. Buna karşın, kardiyak fibrozis de dahil çeşitli fibrotik durumlarda rol oynadığı bilinen galektin-3 ile ilgili yeterli veri yoktur. Bu çalışmada, serum galektin-3 düzeyinin başarılı elektriksel kardiyoversiyon sonrası AF nüksünü öngörmedeki rolü araştırıldı.

Yöntemler: Elektriksel kardiyoversiyon planlanan persistan AF'li 90 hasta çalışmaya alındı. Hastaların serum örneklerindeki galektin-3 seviyeleri elektriksel kardiyoversiyondan önce ELISA yöntemi ile ölçüldü. Hastalar, elektriksel kardiyoversiondan sonra, AF nüksü açısından üç ay süreyle takip edildi.

Bulgular: Başarılı elektriksel kardiyoversiyon uygulanan 90 AF'li hasta (55.33±7.94 yıl; %53.33 erkek) çalışmaya alındı. Üç aylık takip sürecinde 28 (%31.11) hastada erken AF nüksü saptandı. AF nüksü olan hastalarda, daha büyük sol atriyum hacim indeksi (33.35±2.45 ve 29.21±3.08 mL/m^2, p<0.001) ve daha yüksek serum galektin-3 düzeyleri (0.88 [0.52–1.32] ve 0.60 [0.38–0.91] ng/mL, p<0.001) saptandı. Çok değişkenli analizde elektriksel kardiyoversiyon uygulama sayısı (HR: 1.879, %95 GA: 1.052–3.355, p=0.033), sol atriyum hacim indeksi (HR: 1.180, %95 GA: 1.028–1.354, p=0.018) ve serum galektin-3 düzeyleri (HR: 11.933, %95 GA: 1.220–116.701, p=0.033) erken AF nüksünün bağımsız öngördürücüleri olarak bulundu.

Sonuç: Dolaşımda bulunan galektin-3 seviyesi, elektriksel kardiyoversiyon uygulanan hastalarda erken AF nüksüyle ilişkili olabilir.

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Atrial fibrillation (AF) is the most common type of sustained arrhythmia and is associated with significant cardiovascular morbidity and mortality.[1] Direct-current cardioversion (DCCV) is accepted as one of the most effective treatment alternatives for the restoration of sinus rhythm in patients with AF. However, patients who have been successfully cardioverted may experience AF recurrence following DCCV. The precise pathophysiological mechanisms underlying AF recurrence after DCCV have not yet been clearly demonstrated.

In addition to electrical remodeling, it has been proposed that underlying structural changes in the atria may be involved in the perpetuation of AF.[2] Fibrosis has been regarded as the hallmark of structural remodeling occurring in the atria and forming a substrate for electrical reentry.[2] Therefore, assessment of fibrosis associated with remodeling may have important implications regarding successful management, including DCCV.

Galectin-3 is an alpha-galactoside-binding lectin that appears to play an important role in a number of fibrotic conditions, including cardiac fibrosis.[3] The role of galectin-3 in the pathogenesis of cardiac fibrosis involves the recruitment of macrophages, myofibroblasts, and fibroblasts into the myocardium, resulting in cellular proliferation and collagen deposition.[4] Our group previously demonstrated that galectin-3 levels were higher in patients with AF when compared with subjects with sinus rhythm and that this was more prominent in patients with persistent AF.[5]

The objective of this study was to investigate whether serum galectin-3 levels may have a predictive value for early AF recurrence following DCCV.

METHODS

Study population

A total of 90 patients with persistent AF who underwent successful DCCV were enrolled in this prospective study. AF episodes that last >7 days or require termination by cardioversion, either with drugs or by DCCV, were defined as persistent.[1]

Patients who had a history of myocardial infarction/stroke/acute coronary syndrome within the previous 3 months, congenital heart disease, permanent pacemaker/cardioverter-defibrillator implantation, abnormal thyroid function, serum creatinine level in excess of 1.20 mg/dL, autoimmune disease, recent infection, or attempted DCCV and/or AF ablation were excluded from the study. Patients with moderate-severe valvular disease, left ventricular hypertrophy, or heart failure with reduced ejection fraction (<50%) were also not included in the study.

Abbreviations:

AF	*Atrial fibrillation*
BMI	*Body mass index*
CI	*Confidence interval*
DCCV	*Direct-current cardioversion*
ECG	*Electrocardiogram*
HR	*Hazard ratio*
ICTP	*Carboxy-terminal telopeptide of type I collagen*
LA	*Left atrial*
LAA	*Left atrial area (LAA) a*
LAd	*Left atrial diameter*
LAVI	*Left atrial volume index*
LV	*Left ventricular*
MMP	*Matrix metalloproteinase*
ROC	*Receiver operating characteristic*
TIMP	*Tissue inhibitor of matrix metalloproteinase*

Baseline demographic and clinical characteristics, including age, gender, body mass index (BMI), smoking habit, and comorbidities, were recorded for all of the patients. Data related to the diagnosis of AF, including the date of first diagnosis, and oral anticoagulation, rate control, and antiarrhythmic medications, were also recorded. Symptomatic severity of the patients was documented according to the European Heart Rhythm Association score.[6] The duration of AF was defined as the length of time between the date of first diagnosis of AF and date of DCCV. All of the patients underwent a transthoracic echocardiographic examination (TTE) to assess left atrial (LA) size and left ventricular (LV) function, and to exclude valvular and structural heart disease. The left atrial diameter (LAd) measurement was obtained in the parasternal long axis view at end-systole of the LV. Left atrial area (LAA) and LA length were measured in the apical 4-chamber and apical 2-chamber views, respectively. Left atrial volume (LAV) was derived using the biplane area-length method. Both LAA and LAV were measured at LV end-systole. Left atrial volume index (LAVI) was calculated based on the patient's body surface area.[7] LV systolic function was quantified from LV end-diastolic and end-systolic dimensions. All of the patients underwent transesophageal echocardiography to rule out an intracardiac thrombus 24 hours before the DCCV procedure. The study was approved by the local ethics committee and informed consent was obtained from all of the participants included in the study (GO 14/398).

Measurement of serum galectin-3 level

Blood samples were collected prior to sedation for

DCCV and immediately centrifuged and stored at -80°C until testing. The frozen serum samples were rapidly thawed and brought to room temperature of 24°C and assayed for the presence of human galectin-3 using enzyme-linked immunosorbent assay kits (eBioscience, Inc., San Diego, CA, USA) according to the manufacturer's instructions. Serial dilutions of known concentrations of human galectin-3 were used to construct a standard curve of the analytes. The serum level of galectin-3 from the samples was estimated by extrapolation from a log:log linear regression curve determined from the serially diluted human recombinant galectin-3.

Direct-current electrical cardioversion

DCCV with R-wave synchronization was performed under conscious sedation in the coronary care unit. Gel-covered electrodes were placed on the chest: The anode was placed right parasternally in the anterior position and the cathode on the left lateral chest wall on the mid-axillary line. A calibrated defibrillator was used to provide biphasic shocks, with a programmed energy of 200 J for the first shock. After an unsuccessful shock, 2 additional attempts at 200 J were applied at 1-minute intervals. Rhythm was assessed at 10 minutes after DCCV, and only stable sinus rhythm at this time was considered a success.

All of the patients received amiodarone as antiarrhythmic drug therapy during the 3 months of follow-up after DCCV. Amiodarone treatment was initiated 24 hours before the DCCV procedure and a total of dose of 1200 mg was infused intravenously during the cardioversion. Following successful DCCV, oral maintenance therapy was 200 mg 3 times daily during the first week, 200 mg twice daily during the second week, and 200 mg once a day thereafter. The study patients underwent clinical follow-up of an office visit with an electrocardiogram (ECG) performed every month or in the event of symptom recurrence. A 24-hour ambulatory ECG was recorded every month in those who were asymptomatic. Follow-up was performed for 3 months to detect early recurrences. AF ablation was recommended for all of the patients who suffered an early AF recurrence and 26 (92%) of these patients underwent the procedure.

Statistical analysis

Normally distributed continuous parameters were presented as mean±SD and skewed continuous parameters were expressed as median (minimum-maximum). Categorical data were presented as frequencies and percentages and were compared using a chi-square test. Comparisons between baseline characteristics were performed with an independent Student's t-test, the Mann-Whitney rank-sum test, Fisher's exact test, or a chi-square test, as appropriate. Cox regression analysis was performed to determine independent associates of early AF recurrence following DCCV. Receiver operating characteristic (ROC) curve analysis was conducted to identify the sensitivity and specificity of serum galectin-3 level at predicting early AF recurrence following DCCV. Kaplan-Meier survival analysis was performed to demonstrate AF-free survival. Statistical analyses are performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Ninety patients hospitalized for DCCV due to persistent AF who were successfully cardioverted to sinus rhythm (mean age: 55.33±7.94 years; 53.33% male) were enrolled in the current study. Baseline characteristics of the study population are shown in Table 1. The median number of DCCV attempts was 1 (min-max: 1–3) per patient. The serum galectin-3 level differed significantly between patients according to the number of DCCV attempts ($p<0.001$) (Fig. 1). All of the patients were followed up for 3 months after DCCV.

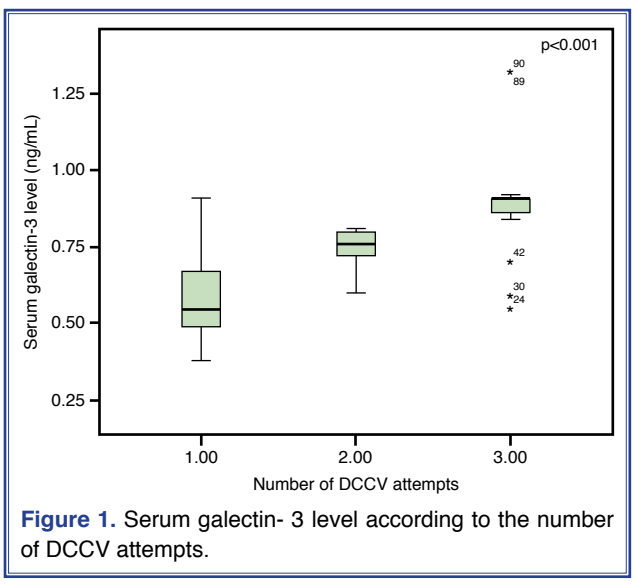

Figure 1. Serum galectin- 3 level according to the number of DCCV attempts.

Table 1. Baseline characteristics of the study population (n=90)

	Study population
Age (years)	55.33±7.94
Gender (male), n (%)	48 (53.33)
BMI (kg/m2)	24.26±2.13
Hypertension, n (%)	30 (33.3)
Diabetes mellitus, n (%)	10 (11.1)
Prior stroke, n (%)	2 (2.2)
Smoking, n (%)	37 (41.1)
Coronary artery disease, n (%)	10 (11.1)
AF duration (months)	6 (1–20)
Number of DCCV attempts (n)	1 (1–3)
EHRA score (1–4)	3 (2–4)
CHA_2DS_2VASc score	1 (0–4)
WBC count (x10^3/μL)	7.50 (3.70–14.20)
BNP (pg/mL)	115 (15.00–691.00)
CRP (mg/dL)	1.40 (0.22–6.78)
LVEDD (cm)	4.96±0.38
LVEF (%)	61.10±4.3
LAd (cm)	4.05±0.47
LAVI (mL/m^2)	30.50±3.47
Galectin-3 (ng/mL)	0.72 (0.38–1.32)

AF: Atrial fibrillation; BMI: Body mass index; BNP: Brain natriuretic peptide; CRP: C- reactive protein; DCCV: Direct-current cardioversion; EHRA: European Heart Rhythm Association; LAD: Left atrial diameter; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; WBC: White blood cell.

Three (3.33%) patients suffered a very early recurrence of AF in the first 24 hours following DCCV. The serum galectin-3 level was higher (0.91 ng/mL [min-max: 0.86–1.32] vs. 0.71 ng/mL [min-max: 0.38–1.32]; p=0.021) in patients with very early AF recurrence. In all, 3 months after DCCV, 28 (31.11%) of the patients who had a successful DCCV suffered an early recurrence of AF. The baseline characteristics of the study population according to early AF recurrence at 3 months are provided in Table 2. The LAVI was greater (33.35±2.45 mL/m^2 vs. 29.21±3.08 mL/m^2; p<0.001) and the serum galectin-3 level was higher (0.88 ng/mL [min-max: 0.52–1.32] vs. 0.60 ng/mL [min-max: 0.38-0.91]; p<0.001) in patients with early AF recurrence. In addition, number of DCCV attempts was higher (1 [min-max: 1–3] vs. 1 [1–3]; p=0.002) and the AF duration was longer (6.50 months [min-max: 2–20] vs. 5 months [min-max: 1–16]; p=0.001) in patients with early AF recurrence. The serum brain natriuretic peptide levels was also higher in patients with early AF recurrence (150.00 pg/mL [min-max: 15.00–691.00] vs. 100.00 pg/mL [15.00–400.00]; p=0.065), but the difference did not reach the level of statistical significance.

Results of Cox regression analysis demonstrating the relationship between baseline characteristics and early AF recurrence are shown in Table 3. Among baseline characteristics, only the number of DCCV attempts (hazard ratio [HR]: 1.879, 95% confidence interval [CI]: 1.052–3.355; p=0.033), LAVI (HR: 1.180, 95% CI: 1.028–1.354; p=0.018), and serum galectin-3 level (HR: 11.933, 95% CI: 1.220–116.701; p=0.033) were found to be independently associated with early AF recurrence at 3 months following DCCV. ROC curve analysis revealed that a serum galectin-3 level ≥0.79 ng/mL predicted early AF recurrence following DCCV with a sensitivity and specificity of 82.0% and 79.0%, respectively (Area under the curve: 0.841, 95% CI: 0.757–0.925; p<0.001). Kaplan-Meier survival analysis revealed significantly lower cumulative survival from early AF recurrence in patients with a serum galectin-3 level ≥0.79 ng/mL (p<0.001) (Fig. 2).

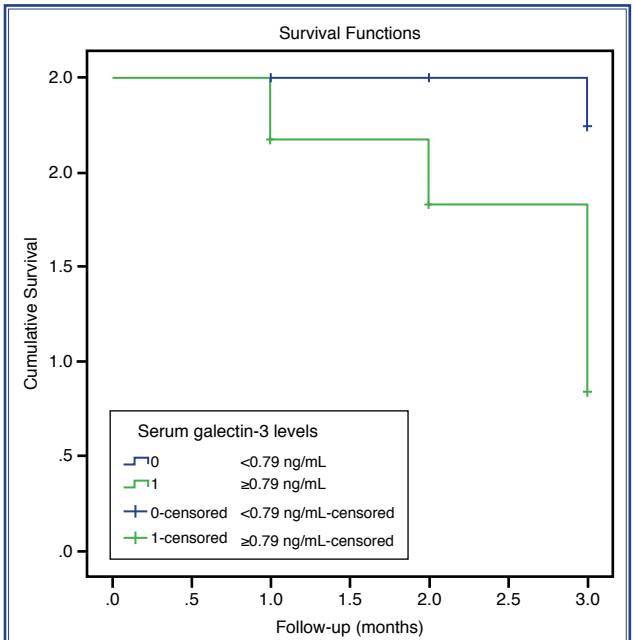

Figure 2. Serum galectin- 3 level and cumulative survival: Kaplan-Meier curve showing atrial fibrillation-free survival during the follow-up period.

Table 2. Baseline and follow-up characteristics of the study population according to atrial fibrillation recurrence (n=90)

	Patients without AF recurrence (n=62)	Patients with AF recurrence (n=28)	*p*
Age (years)	55.11±8.43	55.82±6.85	0.698
Gender (male), n (%)	35 (56.5)	13 (46.4)	0.378
BMI (kg/m^2)	23.98±1.93	24.86±2.44	0.070
Hypertension, n (%)	21 (33.9)	9 (32.1)	0.872
Diabetes mellitus, n (%)	6 (9.7)	4 (14.3)	0.495
Prior stroke, n (%)	2 (3.2)	0	1.000
Smoking, n (%)	23 (37.1)	14 (50.0)	0.249
Coronary artery disease, n (%)	5 (8.1)	5 (17.9)	0.275
AF duration (months)	5 (1–16)	6.50 (2–20)	0.001*
Number of DCCV attempts (n)	1 (1–3)	1 (1–3)	0.002*
EHRA score (1–4)	3 (2–4)	3 (2–4)	0.834
CHA_2DS_2VASc score	1 (0–4)	1 (0–4)	0.772
WBC count (x10^3/μL)	8.10±2.76	8.09±2.42	0.988
BNP (pg/mL)	100.00 (15.00–400.00)	150.00 (15.00–691.00)	0.065
CRP (mg/dL)	1.38 (0.22–5.20)	2.13 (0.24–6.78)	0.085
LVEDD (cm)	4.72±0.37	5.20±0.36	0.435
LVEF (%)	62.50±3.50	60.25±4.50	0.555
LAd (cm)	3.87±0.41	4.45±0.33	<0.001*
LAVI (mL/m^2)	29.21±3.08	33.35±2.45	<0.001*
Galectin-3 (ng/mL)	0.60 (0.38–0.91)	0.88 (0.52–1.32)	<0.001*
Anticoagulation therapy, n (%)			
Warfarin	56 (90.3)	22 (78.6)	0.379
Dabigatran	1 (1.6)	2 (7.1)	
Rivaroxaban	2 (3.2)	1 (3.6)	
Apixaban	3 (4.8)	3 (10.7)	
Time until AF recurrence (days)	–	35 (1–60)	

AF: Atrial fibrillation; BMI: Body mass index; BNP: Brain natriuretic peptide; CRP: C- reactive protein; DCCV: Direct-current cardioversion; EHRA: European Heart Rhythm Association; LAD: Left atrial diameter; LAVI: Left atrial volume index; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction; WBC: White blood cell. *P<0.05.

DISCUSSION

LA interstitial fibrosis is known to modify the pattern of myocyte apposition, causing disarrangement of inter-myocyte connections, altering the cell-to-cell interaction. This results in spatial dispersion of atrial refractoriness and causes inhomogeneous, localized conduction abnormalities, predisposing to initiation and continuance of AF.[8] Our results demonstrated that pre-DCCV serum galectin-3 level was independently associated with early AF recurrence at 3 months follow-up after DCCV.

Recurrence of AF after DCCV cannot be explained solely by persistent changes in ion channel remodeling, since changes in most of these electrogenic processes have been reported to rapidly normalize with restoration of sinus rhythm.[9] Structural remodeling has therefore emerged as an important factor in the perpetuation of AF.

Several studies have investigated the mechanisms that could result in extracellular matrix turnover abnormalities in AF recurrence. Abnormal pre-DCCV indices of matrix degradation (matrix metalloproteinase [MMP] type 1, its tissue inhibitor [TIMP-1], and carboxy-terminal telopeptide of collagen type I [ICTP]) have not been found to be associated with

Table 3. Cox regression analysis demonstrating the relationship between baseline characteristics and post-direct-current cardioversion AF recurrence

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
BMI (kg/m²)	1.208	0.984–1.484	0.071	0.909	0.714–1.157	0.437
AF duration (months)	1.218	1.123–1.321	<0.001*	1.097	0.998–1.205	0.054
Number of DCCV attempts	1.940	1.285–2.930	0.002	1.879	1.052–3.355	0.033*
LAVI (mL/m²)	1.276	1.138–431	<0.001*	1.180	1.028–1.354	0.018*
Galectin-3 (ng/mL)	159.231	22.565–1123.599	<0.001*	11.933	1.220–116.701	0.033*
C-reactive protein (mg/dL)	1.176	0.988–1.399	0.069	1.224	0.988–1.515	0.064
BNP (pg/mL)	1.003	1.000–1.005	0.032	1.003	1.000–1.006	0.057

AF: Atrial fibrillation; BMI: Body mass index; BNP: Brain natriuretic peptide; CI: Confidence interval; DCCV: Direct current cardioversion; HR: Hazard ratio; LAVI: Left atrial volume index. *P<0.05.

the immediate DCCV success.[10] In the same study, maintenance of sinus rhythm at 1 month was found to be associated with lower C-reactive protein and ICTP levels.[10] In another study, MMP-9, MMP-3, and TIMP-4 were found to be independent predictors of AF recurrence following DCCV.[11] Kawamura et al.[12] reported elevated baseline type III procollagen-N-peptide concentration as an independent predictor of AF recurrence after electrical or pharmacological cardioversion.

The relationship between extracellular matrix turnover markers and AF recurrence has also been evaluated following other interventions for rhythm control, including pharmacological cardioversion and ablation. Kato et al.[13] reported that a higher pre-procedural plasma level of MMP-2 was predictive of AF recurrence in patients undergoing pharmacological cardioversion. Okumura et al.[14] observed that the plasma MMP-2 level was higher in AF patients with recurrence following ablation.

Galectin-3 is a member of the galectin family, which comprises β-galactoside lectins.[15] It has been shown to play a central role in fibrosis and tissue remodeling.[15] An increase in galectin-3 is known to stimulate the release of various mediators, such as transforming growth factor beta 1, and to promote cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction.[3] Increased plasma levels of galectin-3 were detected in failure-prone hypertrophied rat and human hearts,[3] as well as in patients with acute and chronic heart failure,[16] suggesting that circulating galectin-3 could be useful in identifying patients at risk for developing cardiac remodeling, and consequently, a poor prognosis.[16] Similar to its demonstrated role in ventricular remodeling, we previously demonstrated that galectin-3 is also associated with atrial structural and electrical remodeling based on its correlation with the extent of LA fibrosis and atrial electromechanical delay in patients with AF.[17] Our current study has shown that the serum galectin-3 level is also associated with early AF recurrence following DCCV. Contrary to our results, Begg et al.[18] found that serum galectin-3 level was not predictive of AF recurrence after DCCV. The study population was composed of mostly males and the participants were older and had a higher BMI in that study when compared with our study group. These differences between the baseline characteristics of the study groups, which may affect serum galectin-3 level,[19] and the longer follow-up in the study by Begg et al. (mean: 383±54 days) might be responsible for this discrepancy in the results of these 2 studies.

LA enlargement is accepted as another core process involved in atrial structural remodeling in addition to fibrosis. Nedios et al.[20] demonstrated that LA enlargement was more prominent in persistent AF patients when compared with paroxysmal AF. Severe LA enlargement is known to be a poor prognostic factor for maintenance of sinus rhythm following DCCV.[21] The results of our study also demonstrated that LAVI was independently associated with AF recurrence following DCCV. LA size is also a well-recognized risk factor for AF recurrence following

other interventions for rhythm control, including cryoballoon-based AF ablation.[22]

This study is limited by its small population. Levels of other extracellular matrix turnover markers, such as MMP or TIMP, were not measured. Therefore, it is uncertain whether galectin-3 is better than the MMPs and TIMPs in the prediction of early AF recurrence. Also, LA fibrosis was not quantified with a direct method, such as delayed enhancement magnetic resonance imaging. Another limitation is that the study lacks detailed echocardiographic parameters that can be associated with AF recurrence, such as LA global longitudinal strain.

Ethics Committee Approval: The study protocol was approved by the local ethics committee (GO 14/398).

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Conflict-of-interest: Dr. Yorgun has received personal fees from Medtronic, Abbott, Biosense, outside the submitted work. Dr. Aytemir has received personal fees from Abbott, Medtronic, Biosense Webster outside the submitted work. Dr. Canpolat has received personal fees from Abbott, Medtronic, outside the submitted work. Dr. Ates, Dr. Guc, Dr. Kocyigit, Dr. Canpinar, Dr. Gurses and Dr. Yalcin have nothing to disclose.

Authorship contributions: Concept: K.M.G., M.U.Y., D.K., H.Y., K.A.; Design: K.M.G., M.U.Y., D.K., H.C., A.H.A., U.C., H.Y., D.G., K.A.; Supervision: H.Y., D.G., K.A.; Materials: K.M.G., M.U.Y., D.K., H.C., A.H.A., U.C., H.Y., D.G., K.A.; Data: K.M.G., M.U.Y., D.K., H.C., A.H.A., U.C., H.Y., D.G., K.A.; Analysis: K.M.G., M.U.Y., D.K., H.Y., U.C.; Literature search: K.M.G., M.U.Y., D.K., A.H.A., U.C., H.Y.; Writing: K.M.G., M.U.Y., D.K., H.C., U.C., H.Y.; Critical revision: K.M.G., M.U.Y., D.K., H.C., A.H.A., U.C., H.Y., D.G., K.A.

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