Potential Biomarkers in Atrial Fibrillation: Insight Into Their Clinical Significance

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Abstract: In risk-stratifying patients with atrial fibrillation (AF), physicians rely heavily on clinical parameters that provide risk scores and determine treatment strategies. There has been increasing research on potential biomarkers in the blood that could more accurately determine both risk of complications in AF and risk of incidence of AF. This review highlights the clinical significance of 5 novel biomarkers that have been shown to be linked to AF. These biomarkers are carbohydrate antigen 125, galectin-3, growth differentiation factor-15, a member of the interleukin 1 receptor family, IL1RL1 (ST2), and N-terminal pro B-type natriuretic peptide.

Key Words: atrial fibrillation, carbohydrate antigen 125, galectin-3, growth differentiation factor-15, suppression of tumorigenicity 2, N-terminal pro B-type natriuretic peptide, biomarker

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BACKGROUND

Atrial fibrillation (AF) is a common arrhythmia encountered in clinical practice.[1] Risk factors predisposing individuals to AF include advancing age, hyperthyroidism, hypertension, obesity, and cardiovascular conditions, such as coronary artery disease, valvular heart disease, and heart failure.[2] Adverse consequences of AF are related to decreased cardiac output and atrial thrombus formation.[3] The pathophysiology of AF is complex and not clearly understood. Accumulating evidence suggests that there is a link between oxidative processes and AF. During episodes of AF, substantial oxidative damage in the atrial myocardium may contribute to atrial remodeling.[4,5] Various inflammatory markers and mediators have been independently linked to AF suggesting a strong association between inflammation and arrhythmia.[6]

There is ongoing search for a novel member of the interleukin 1 receptor family, IL1R1 (ST2) biomarkers that can help in risk stratification or in being of prognostic value for patients with AF. This review discusses the clinical significance of 5 novel biomarkers in the diagnosis and prognosis of AF. These biomarkers are carbohydrate antigen 125 (CA-125), galectin-3 (Gal-3), growth differentiation factor-15 (GDF-15), a member of the interleukin 1 receptor family, IL1R1 (ST2), and N-terminal pro B-type natriuretic peptide (NT-proBNP).

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METHODS

Data presented in this review were selected after an extensive and comprehensive search of the English literature through MEDLINE and PubMed. Different keywords and MeSH terms related to AF, CA-125, Gal-3, GDF-15, ST2, and NT-proBNP were combined using the "OR" and "AND" operators. All studies pertaining to humans were included. Only studies including a representative population sample and evaluating the different biomarkers in relation to AF were included. Conference proceedings were excluded. Other published articles were identified by cross-checking cited references.

CA-125

CA-125 also known as cancer antigen 125 is a glycoprotein encoded by the *MUC16* gene.[7] CA-125 is produced by epithelial cells of coelomic origin such as pleural, pericardial, and peritoneal cells specifically after mechanical stress or in an inflammatory setting.[8] It is a well-established tumor biomarker in ovarian cancer and associated with other malignancies and benign conditions. Most recently, CA-125 has been linked to cardiovascular disease, mainly heart failure.[9,10] Durak-Nalbantic et al[9] found a significant elevation of CA-125 levels in patients with decompensated heart failure compared with patients with compensated heart failure. Increased CA-125 levels, along with high levels of BNP, can increase sensitivity in identifying patients at risk for acute heart failure and can potentially affect management, such as increasing diuresis. Yilmaz et al collected data on 150 patients who had a CA-125 level and an echocardiogram performed within 1 week of CA-125 sampling. Reduced ejection fraction, presence of right ventricular dilatation, and presence of pericardial effusion each independently predicted elevated CA-125 levels.[10] These results further emphasize a potential prognostic role of CA-125 level in patients with heart failure. Recent studies have focused on finding a correlation between CA-125 levels and AF. In a cohort of heart failure patients, Durak-Nalbantic et al[9] noted significant elevation in CA-125 levels in patients with AF compared with patients with normal sinus rhythm. Furthermore, CA-125 levels in systolic heart failure patients were associated with the presence of permanent AF and new-onset AF.[11,12] Yilmaz et al[10] found that AF was significantly more common in patients with elevated levels of CA-125 compared with those with normal levels of CA-125. In a comparative study between patients with AF and normal controls, De Gennaro et al[13] found no statistically significant difference in CA-125 levels between the 2 groups, and no significant difference in CA-125 levels between patients with AF duration longer than 6 months compared with those with less than 6 months AF duration. However, in the AF group, higher CA-125 levels were associated with higher NHYA classes, providing that CA-125 may be associated with impaired functional class in AF.[13] In a study conducted by Sekiguchi et al[14] on postmenopausal women, it was found that patients with new-onset AF had significantly higher CA-125 levels compared with normal controls. Studies performed on CA-125 and AF are summarized in Table 1. The preposed mechanisms leading to elevated levels of Ca-125 in cardiovascular diseases, including AF, have been attributed to weakened ventricular function, left atrial remodeling, and mechanical and oxidative vascular stress.[15,16] In addition, the prothrombotic state and general systemic inflammatory response seen in AF leads to the increased production of cytokines such as IL-6, TNF-α, IL-8, and IL-10 triggering the release of Ca-125 from the epithelial coelomic cells of the serosal tissue.[17]

Gal-3

Gal-3 belongs to the family of mammalian lectins that have an affinity to β-galactosides. It is found in the cytoplasm, extracellular space, and bound to the cell surface[18] and expressed by myocytes, fibroblasts, endothelial cells, and inflammatory cells, such as macrophages.[19–23] It mediates cell-to-cell and cell-to-matrix interactions and acts as a chemoattractant to monocytes and macrophages.[24] Studies have shown that Gal-3 is in fact involved in cardiac dysfunction through induction of cardiac fibroblast proliferation, collagen deposition, and ventricular dysfunction.[25,26]

Atrial interstitial fibrosis is a substrate for AF, and sustained AF in return contributes to both electrical and structural cardiac remodeling. Because of the major role of Gal-3 in cardiac fibrosis, studies have sought to find an association between circulating levels of Gal-3 and the incidence of AF. The incidence of AF in the community has been assessed in a 10-year cohort on participants from the Framingham offspring cohort.[27] Two hundred fifty (7.6%) participants developed AF over 10 years. This value, however, is not representative of the whole population because most the participants were White. After age-adjusted and sex-adjusted analyses, a higher concentration of Gal-3 was associated with an increased risk of developing AF over 10 years. However, when adjusted for other known cardiac risk factors such as elevated systolic and diastolic blood pressures, diabetes mellitus, and smoking, the association was no longer significant. The results of this study therefore did not support the use of Gal-3 in predicting future AF.[27]

Recent studies have focused on AF and atrial remodeling and their relation to serum concentration of Gal-3 in attempt to use it for prognostic purposes. Yalcin et al[28] found a significant correlation between Gal-3 levels and the extent of left atrial fibrosis evaluated by delayed enhancement magnetic resonance imaging in patients with paroxysmal AF and preserved left ventricular function, further demonstrating Gal-3's role in atrial fibrosis. Several studies have shown that Gal-3 serum levels are elevated in patients with AF compared with healthy controls.[29–32] Levels of Gal-3 in persistent AF have also been shown to be higher in persistent AF as opposed to paroxysmal AF.[30–33] In addition, after cardiac surgery, patients with persistent AF have been shown to have higher Gal-3 levels than patients with aortic valve or ischemic heart disease.[34] Chen et al[35] showed higher Gal-3 levels in new-onset AF over chronic AF

Studies have also shown a predictive potential of Gal-3 levels in the risk of developing AF. Patients with elevated Gal-3 have been shown to be at higher risk for new-onset AF.[36] Patients without heart failure hospitalized for a first myocardial infarction and treated with primary percutaneous stents were also at higher risk for new-onset AF if they had higher Gal-3 levels.[37] Gal-3 has also been shown to have predictive value in AF recurrence after ablation. Patients who underwent AF thoracoscopic surgical ablation were more likely to develop recurrent AF if Gal-3 levels were elevated from their baseline levels compared with patients who had similar or decreased Gal-3 levels.[37] This study noted the importance of the change in Gal-3 value rather than the baseline value itself in predicting recurrence of AF. Wu et al and Clementy et al similarly demonstrated that elevated Gal-3 levels after AF ablation predicted recurrence.[32,38] A study performed on sheep models that had tachypacing-induced AF showed that inhibiting Gal-3 with Gal-3 inhibitor GM-CT-01 decreased atrial fibroblast migration and also decreased atrial dilatation, myocyte hypertrophy, and fibrosis. Gal-3 inhibitors may reduce AF progression. Hence, they may be useful in decreasing the risk of recurrent AF after catheter ablation.[39] Other studies found no predictive potential of Gal-3 in AF recurrence after external direct current cardioversion or catheter ablation.[40,41] Kocygit et al went on to further show that serum Gal-3 levels are associated with left atrial appendage flow velocity and the presence of spontaneous echo contrast, indicating a potential role of Gal-3 in risk stratification for thromboembolism in patients with persistent AF.[42] A summary of the studies conducted on Gal-3 and AF is presented in Table 2.

There are sufficient studies that demonstrate the important role of Gal-3 in cardiac fibrosis, inflammation, and subsequent cardiac remodeling. Gal-3 may also play a role in predicting AF occurrence and reoccurrence after ablation. The therapeutic role of Gal-3 inhibition in the possible decrease in cardiac remodeling and therefore the development of AF deserves further research for clinical applicability.

TABLE 1. Summary of CA-125 and AF Studies

Study	Study Design	Patient Characteristics: Age (Mean yrs ± SD)	Gender (% Female)	LVEF (% ± SD)	Group 1	Group 2 (Control)	Outcome	Results	*P*
Durak-Nalbantic et al[9]	Cross-sectional study	73.50 ± 12.5	44%	37.14 ± 10.19	26 patients with HF and AF	24 patients with HF and NSR	CA-125 level	Group 1: 98.40 (48.20–242.70) U/mL Group 2: 47.30 (12.95–99.05) U/mL	0.015
Kaya et al[12]	Retrospective cohort	68 ± 11	29%	31.7 ± 8.3	67 patients with stable systolic HF and AF	138 patients with stable systolic HF and normal NSR	CA-125 level	Group 1: 102 (7–269) U/mL Group 2: 33 (3–273) U/mL	<0.001
Yucel et al[11]	Prospective cohort (follow-up 22.1 ± 11 mo)	61 ± 10	29%	33 ± 7	36 patients who developed AF in the follow-up period after hospitalization for systolic HF	113 patients with NSR in the follow-up period after hospitalization for systolic HF	CA-125 level	Group 1: 99 U/mL (48–172) Group 2: 47 U/mL (18–108)	0.001
Yilmaz et al[10]	Prospective cohort (follow-up 8 mo; range 2–42)	Elevated CA-125 group: 0.6 ± 12.7 Normal CA-125 group: 69.9 ± 10.7	46% female	Elevated CA-125 group: 42 ± 15 Normal CA-125 group: 51 ± 14	52 patients with an elevated CA-125 level followed up for development of AF	82 patients with a normal CA-125 level followed up for development of AF	Development of AF	Group 1: 51.9% Group 2: 13.4%	<0.001
De Gennaro et al[13]	Cross-sectional study (follow-up 10 yr)	58 ± 9	54%	—	48 patients with AF	58 patients with NSR	CA-125 level	Group 1: 31.85 U/mL SD 41.95 Group 2: 29.47 U/mL SD 72.01	0.843
Sekiguchi et al[14]	Prospective cohort (10 yr follow-up)	AF group: 75 ± 6 yr NSR group: 67.7 ± 7.7	100%	>55%	31 postmenopausal patients with AF	715 postmenopausal patients with NSR	CA-125 levels	Group 1: 11.4 U/mL SD 6.3 Group 2: 7.7 U/mL SD 3.2	<0.01

NSR, normal sinus rhythm.

GDF-15

GDF-15 belongs to the transforming growth factor β superfamily. It is weakly expressed in all tissues except the placenta[43] but is upregulated by the myocardium in response to increased myocyte stretch, volume overload, oxidative stress, and inflammatory state.[44–46] It has been shown by studies in GDF-15 gene-targeted mice that GDF-15 has antiapoptotic, antihypertrophic, and antiremodeling effects on the heart.[45,46] GDF-15 has also been shown increased in patients with paroxysmal and incident AF compared with healthy controls.[44,47] Svennberg et al[48] described this link between AF and GDF-15 but noted a blunted association when N-terminal pro-BNP is included in the analysis. AF was also more common in patients with heart failure and patients with hypertrophic cardiomyopathy who had elevated GDF-15 levels.[49,50] In a study on patients with rheumatic heart disease, patients with AF had increased serum levels of GDF-15 and increased GDF-15 mRNA levels in atrial tissue. GDF-15 was positively correlated with cardiac fibrosis.[51] GDF-15 has also been shown to have prognostic value in patients with AF. GDF-15 was found to be a risk factor for major bleeding, stroke, and mortality in patients with AF on anticoagulation.[52–54] In addition to increased inflammation and oxidative stress, the association between GDF-15 and the risk of bleeding might be attributed to its inhibitory effect on platelet activation mediated through a mechanism similar to glycoprotein IIb/IIIa inhibition, leading to an impaired ability to form thrombus.[55] With other factors including age, history of bleeding, and hemoglobin levels, GDF-15 may prove useful in the decision of anticoagulation treatment. In a cohort of Chinese patients with nonvalvular AF, Liu et al[54] did not find significant differences in GDF-15 expression in low/intermediate CHA_2DS_2-VASc risk compared with high-risk patients and

TABLE 2. Summary of Galectin-3 and AF Studies

Study	Study Design	Patient Characteristics: Age (Mean ± SD years)	Patient Characteristics: Gender (% Female)	Patient Characteristics: LVEF (Mean % ± SD)	Outcome	Group 1	Group 2	Results	*P*
Ho et al[27]	Prospective cohort from the Framingham offspring cohort (follow-up 10 yr)	58 ± 9	54%	—	Hazard ratio of AF (HR, 95% CI)	250 patients who developed AF	1072 patients who did not develop AF	In age-adjusted and sex-adjusted analyses: HR: 1.19, 95% CI (1.05–1.36)	0.009
								In adjustment for traditional clinical AF risk factors: HR: 1.12, 95% CI (0.98–1.28)	0.10
Yalcin et al[28]	Cross-sectional study	58	48.5%	65.3 ± 2.6	Correlation between Gal-3 levels and LA fibrosis (determined with DE-MRI)	33 patients with paroxysmal AF and preserved LV function	None	(B ± SE: 0.549 ± 7.745; 95% CI: 16.874–47.550)	<0.001
Gurses et al[29]	Cross-sectional study	57.6 ± 11.1	53.3%	65.9 ± 3.5	Gal-3 level	76 patients with preserved LV systolic function	75 patients with age and gender-matched controls	Group 1: median 0.6 ng/mL (interquartile range 0.2–1.4)	<0.001
						Group 1a: 42 with paroxysmal AF		Group 2: median 0.5 ng/mL (interquartile range 0.1–0.7)	
						Group 1b: 34 with persistent AF		Group 1a: median 0.5 ng/mL (interquartile range 0.2–0.9)	<0.001
								Group 1b: median 0.8 ng/mL (interquartile range 0.4–1.4)	
Selcoki et al[30]	Cross-sectional study	59.1 ± 7.7	52.2%	63.7 ± 3	Gal-3 level	46 patients with paroxysmal AF and preserved LV systolic function	38 patients with age-matched and gender-matched controls	Group 1: median 1.38 ng/mL (1.21–1.87)	<0.001
								Group 2: median 1.21 ng/mL (0.88–1.37)	
Wu et al[32]	Prospective cohort (mean follow-up, ± SD): 17 ± 4.1 mo)	46.1 ± 10.7	4.3%	64.0 ± 4.5	Gal-3 level	50 patients with persistent AF	46 healthy patients with NSR	Group 1: 5.40 ng/mL ± 2.24	<0.001
						Group 1a: 18 patients with recurrent AF after ablation		Group 2: 3.63 ng/mL ± 1.18	
						Group 1b: 32 patients without recurrent AF after ablation		Group 1a: 6.03 ng/mL ± 2.12	0.007
								Group 1b: 4.28 ng/mL ± 2.03	

(*continued on next page*)

TABLE 2. (*Continued*) Summary of Galectin-3 and AF Studies

Study	Study Design	Patient Characteristics: Age (Mean ± SD years)	Gender (% Female)	LVEF (Mean % ± SD)	Outcome	Group 1	Group 2	Results	*P*
Hernández-Romero et al[34]	Cross-sectional study	65.1 ± 9.5	23%	—	Gal-3 level	15 patients with permanent AF who underwent cardiac surgery	100 patients with aortic valve disease or ischemic heart disease who underwent cardiac surgery	Group 1: 17.61 ± 6.84 ng/mL Group 2: 14.25 ± 4.15 ng/mL	0.02
Chen et al[35]	Cross-sectional study	68 ± 11	40%	>45	Gal-3 level	32 patients with new-onset AF	99 patients with chronic AF	Group 1: 9.4 ng/mL ± 3.3 Group 2: 8 ng/mL ± 3.3	0.04
Szadkowska et al[37]	Cross-sectional study	62.1 ± 10.3	28.3% f	—	% of patients who developed AF	36 patients who underwent primary percutaneous coronary intervention after first acute MI and have levels of Gal-3 > 16 ng/mL	109 patients who underwent primary percutaneous coronary intervention after first acute MI and have levels of Gal-3 ≤ 16 ng/mL	Group 1: 19.4% Group 2: 2.7%	<0.05
Clementy et al[38]	Prospective Cohort (follow-up 12 mo)	61 ± 10	29%	54 ± 11	Gal-3 levels	55 patients who underwent AF ablation and recurrent AF	105 patients who underwent AF ablation and did not have recurrent AF	Group 1: 14.4 ng/mL ± 5.6 Group 2: 13.5 ng/mL ± 4.8	0.01
Kornej et al[41]	Prospective cohort	62 ± 9	35%	60 ± 8	Gal-3 levels	36 patients who had late recurrent AF after AF radiofrequency catheter ablation	56 patients who did not have late recurrent AF after AF radiofrequency catheter ablation	Group 1: 7.09 ng/mL ± 2.75 Group 2: 8.11 ng/mL ± 3.13	0.111

DE-MRI, delayed enhancement magnetic resonance imaging; HR, hazard ratio; LA, left atrium; LV, left ventricle; MI, myocardial infarction.

further discussed that GDF-15 may be independently linked to stroke risk apart from this risk score. Furthermore, a study on participants in the Framingham Heart Study did not show any association between GDF-15 levels and incident AF when adjusting for AF risk factors, BNP, and C-reactive protein.[56]A summary of the studies conducted on GDF-15 and AF is presented in Table 3.

With the current research, GDF-15 may be of prognostic value because it has been shown to be a risk factor in AF complications. Serum levels, along with other factors, may prove to be useful in risk stratification in patients with AF.

ST2

IL1RL1 encodes a member of the interleukin 1 receptor family (ST2). It exists in a membrane-bound form (ST2L) and a soluble form (sST2). sST2 serves as a decoy and blocks the interleukin (IL)-33-ST2L signaling pathway inhibiting inflammatory gene transcription and inflammatory cytokine release and immunologic response.[57] Therefore, the higher the level of IL-33 production and activity, the higher the serum sST2 levels are in response. The IL1RL1gene has been shown to be upregulated during myocyte stretch, and its importance has been studied in heart failure.[35] In addition, the signaling pathway elicited by (IL)-33-ST2L has been implicated in vascular endothelial cell inflammation and remodeling.[58–60] Because of the interplay between heart failure, cardiac remodeling, and AF, it is suspected that sST2 could be a predictor of AF incidence and may carry prognostic value. In patients with heart failure with preserved ejection fraction, sST2 levels were shown to be associated with the presence of AF.[61] However, in a study on participants in the Framingham Heart Study, sST2 showed no significant association with the incidence of AF.[56] Although the association between sST2 and the incidence of AF may be unclear, sST2 has been shown to have a potential prognostic role in AF. In a study on patients with permanent AF on anticoagulation, sST2 levels were proved to be independently associated with mortality, even after adjusting for the CHA_2DS_2-VASc score.[62] Finally, a study by Okar et al studied the association between sST2 and recurrence of nonvalvular paroxysmal AF after cryoballoon catheter ablation and found that sST2 is the only independent parameter for predicting AF recurrence (odds ratio, 1.085; $P = 0.001$). In other words, for every 10-unit

TABLE 3. Summary of GDF-15 and AF Studies

Study	Study Design	Patient Characteristics: Age (Mean years ± SD)	Gender (% Female)	LVEF (% ± SD)	Group 1	Group 2 (Control)	Outcome	Results	*P*
Shao et al[44]	Cross-sectional study	66.1 ± 10.3	58.2%	60.93 ± 5.58	67 patients with paroxysmal AF	67 patients with NSR	GDF-15 level	Group 1: 1473.14 ± 628.52 pg/mL Group 2: 1233.59 ± 262.76 pg/mL	<0.05
Chan et al[49]	Prospective cohort (median follow-up of 23 mo)	61 ± 12	24%	—	916 patients with heart failure HFrEF and HFpEF	None	Multiple linear regression (AF and GDF-15 level)	Coefficient: 0.093	0.0033
Montoro-García et al[32]	Cross-Sectional study	47.1 ± 14.6	27%	—	102 patients with HCM	None	Association between AF and GDF-15 levels by the Mann–Whitney test:	Z Mann–Whitney: −2.50	0.012
Liu et al[54]	Cross-sectional study	Low-intermediate–risk group: 56.1 ± 10.9 High-risk group: 71.5 ± 7.5	51.9%	59.35 ± 10.41	28 patients with nonvalvular AF and a low-intermediate–risk CHA_2DS_2-VASc score	76 patients with nonvalvular AF and a high-risk CHA2DS2-VASc score	GDF-15 level	Group 1: 1351 ng/mL ± 527.61 Group 2: 1460 ± 623.91	0.415
Rienstra et al[56]	Prospective cohort: 10 yr follow-up of participants of the Framingham Heart Study	59 ± 10	54%	—	242 participants who developed AF	2975 participants who did not develop AF	Hazard ratio of AF (HR, 95% CI)	AF risk after adjusting for risk factors, BNP, CRP: HR = 1.05 (0.91–1.21)	0.49

HCM, hypertrophied cardiomyopathy.; HR, hazard ratio; NSR, normal sinus rhythm; OR, odds ratio

increase in sST2 levels, the risk of AF recurrence increases by 2.103-fold.[63] Although sST2 has not been proven to be associated with the incidence of AF, it served as a prognostic tool to predict AF recurrence after ablation. The latter finding can be explained by the difference in pathophysiology of AF and AF recurrence. The incidence of AF is related to pulmonary vein triggers[64] but recurrence after ablation is usually related to reconnection of pulmonary veins and AF originating from larger areas of the atrium facilitated by structural and electrical remodeling, fibrosis, and inflammation resulting from inflammatory signaling pathways, including (IL)-33-ST2L.[63,65]

Further research is needed to determine whether there is a link between the risk or presence of AF and sST2 levels. More studies are needed to further demonstrate the role sST2 may have in risk stratification of patients with AF and prognosis after ablation.

NT-proBNP

BNP is a molecule produced by heart ventricles in response to increased mechanical load and wall stretch.[66] Both BNP and NT-proBNP are important prognostic indicators in heart failure.[67] However, increased plasma levels are not specific for heart failure and are influenced by a variety of cardiac and noncardiac conditions seen in the intensive care setting.[68] There is increasing interest in the role of NT-proBNP in predicting AF risk and risk-stratifying patients with AF. Patton et al[69] studied 5445 Cardiovascular Health Study participants and found that NT-proBNP levels were strongly associated with prevalent AF and were strong predictors of incident AF after adjusting for multiple risk factors. Ellinor et al discovered that patients with lone AF had elevated NT-proBNP levels, even when in normal sinus rhythm. In addition, these patients had normal proatrial natriuretic peptide levels, and the authors determined that elevated NT-proBNP levels combined with normal proatrial natriuretic peptide levels were associated with lone AF and underlying predisposition to developing it.[70] Letsas et al[71] also supported this by demonstrating elevated NT-proBNP levels in patients with paroxysmal and permanent AF compared with those with sinus rhythm in the setting of preserved left ventricular systolic function.

CONCLUSION

There is ongoing search for novel biomarkers that may predict AF risk and carry prognostic value. CA-125, Gal-3, GDF-15, sST2, and NT-proBNP have all been linked to incidence and risk stratification of AF. Some of the above markers reflect the pathophysiologic process of AF, whereas others are simple markers of severity or comorbidity that relates to an increased risk of AF. Although most of the markers were shown to be elevated in AF, the optimal utility of these biomarkers depends on the different subgroups of patients and setting. In heart failure, CA-125, NT-ProBNP, and GDF-15 are effective in predicting the presence of new-onset AF,[9,49,50] whereas Gal-3 and sST2 best predict recurrence of AF after ablation.[38,63] Apart from predicting incidence, GDF-15 and sST2 also have prognostic utility serving as independent risk factors for stroke and mortality, respectively.[54,62] Finally, biomarkers were shown to be of use in the treatment selection of AF by studies focusing on the association of Gal-3 levels and bleeding risk with anticoagulation.[54,55] Further investigation is warranted to better understand the pathophysiology of AF and its interplay with the proposed biomarkers to establish their use in multimarker-based risk stratification, treatment surveillance, targeted therapy, and early detection.

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