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CONTEMPORARY REVIEW

Characterization, Pathogenesis, and Clinical Implications of Inflammation-Related Atrial Myopathy as an Important Cause of Atrial Fibrillation

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ABSTRACT: Historically, atrial fibrillation has been observed in clinical settings of prolonged hemodynamic stress, eg, hypertension and valvular heart disease. However, recently, the most prominent precedents to atrial fibrillation are metabolic diseases that are associated with adipose tissue inflammation (ie, obesity and diabetes mellitus) and systemic inflammatory disorders (ie, rheumatoid arthritis and psoriasis). These patients typically have little evidence of left ventricular hypertrophy or dilatation; instead, imaging reveals abnormalities of the structure or function of the atria, particularly the left atrium, indicative of an atrial myopathy. The left atrium is enlarged, fibrotic and noncompliant, potentially because the predisposing disorder leads to an expansion of epicardial adipose tissue, which transmits proinflammatory mediators to the underlying left atrium. The development of an atrial myopathy not only leads to atrial fibrillation, but also contributes to pulmonary venous hypertension and systemic thromboembolism. These mechanisms explain why disorders of systemic or adipose tissue inflammation are accompanied an increased risk of atrial fibrillation, abnormalities of left atrium geometry and an enhanced risk of stroke. The risk of stroke exceeds that predicted by conventional cardiovascular risk factors or thromboembolism risk scores used to guide the use of anticoagulation, but it is strongly linked to clinical evidence and biomarkers of systemic inflammation.

Key Words: atrial fibrillation ■ atrial myopathy ■ stroke

Historically, long-standing atrial fibrillation (AF) has been observed in clinical settings that are characterized by prolonged hemodynamic stress. The most common risk factor for AF in the general population is hypertension, and in these patients, left ventricular (LV) hypertrophy followed by left atrial (LA) enlargement creates the anatomical substrate for AF. Activation of the renin-angiotensin system contributes to the genesis of AF in these patients; in randomized controlled trials, the treatment of patients with hypertension or LV hypertrophy with drugs that inhibit the renin-angiotensin system ameliorates the burden of AF.[1] Additionally, mitral or aortic valvular disease or LV systolic dysfunction can also produce sustained increases in LA pressure, producing a fertile substrate for AF. Alleviation of the hemodynamic stresses (eg, with corrective valve surgery) can reduce the prevalence of AF in many patients[2]; yet, in others, the deranged LA anatomical substrate for AF is not effectively ameliorated by the procedure.

However, during the past several decades, many patients who have AF do not have evidence of a disorder that causes hemodynamic stresses on the left atrium. These patients have echocardiograms that typically reveal no evidence of meaningful valvular abnormalities or dilatation, hypertrophy or impairment of the systolic function of the left ventricle. In these individuals, cardiac imaging commonly reveals abnormalities of the structure or function of the atria, particularly the left atrium. The left atrium is enlarged, and it often exhibits impaired emptying as well as derangements in its reservoir and conduit functions.[3] Abnormalities of LA structure predict the development of AF independent of a history of hypertension, heart failure, or

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myocardial infarction.[4] These patients have an atrial myopathy, and its most clinically evident manifestation is AF (Figure 1).

SYSTEMIC INFLAMMATORY AND METABOLIC DISORDERS CAUSE AN ATRIAL MYOPATHY THAT CAN LEAD TO AF

Many patients who have AF that is related to an atrial myopathy have evidence of long-standing inflammation initiated at a site that resides outside of the cardiovascular system. Biomarkers of systemic inflammation are a common precedent of AF in the general community,[5] and systemic inflammation predicts the evolution and development of adverse atrial remodeling.[6] The systemic inflammatory process can be triggered in 2 ways.

First, many chronic systemic inflammatory (often autoimmune) diseases are accompanied by an LA myopathy and an increased risk of AF. Specifically, rheumatoid arthritis is accompanied by an ≈40% increase in the incidence of AF,[7] and this risk is evident even after adjustment for traditional risk factors for AF (eg, hypertension). Similarly, the incidence of AF is increased by ≈40% in patients with psoriasis[8]; the risk is particularly apparent in those who are young or have clinically severe inflammatory disease. In both disorders, electrocardiography shows abnormalities of electrical activation in the atria, with evidence of electromechanical delay. Cardiac imaging studies confirm the presence of significant abnormalities in atrial geometry and filling characteristics (particularly the left atrium), which are consistent with an extension of the systemic inflammatory process to the atrial wall. In a similar manner, the incidence and prevalence of AF is increased in systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, inflammatory bowel disease, and chronic pulmonary inflammation.[9–12] Many patients with these disorders have structural or functional evidence of an atrial myopathy (Figure 2).[13,14]

Second, a broad range of metabolic disorders that are characterized by adipose tissue inflammation are also accompanied by an increased risk of AF. Obesity dramatically increases the incidence and prevalence of AF,[15] and the burden of AF is meaningfully reduced by bariatric surgery. Type 2 diabetes mellitus is accompanied by an increased risk of AF, which is proportional to the degree of poor glycemic control.[16] Other states of adipose tissue inflammation and insulin resistance are accompanied by an increased risk of AF; these include the metabolic syndrome and non-alcoholic liver disease[17,18] as well as hormonal diseases that promote

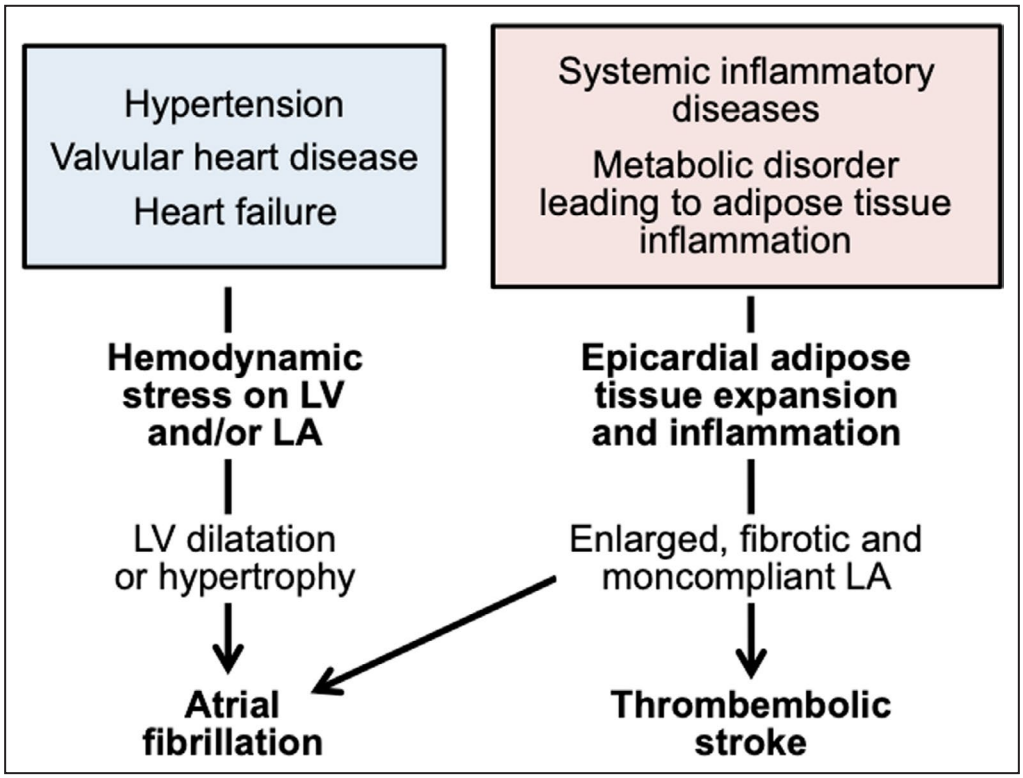

Figure 1. Hemodynamic and inflammatory stresses can lead to atrial fibrillation by distinct pathophysiological pathways.
LA indicates left atrium; LV, left ventricle or left ventricular.

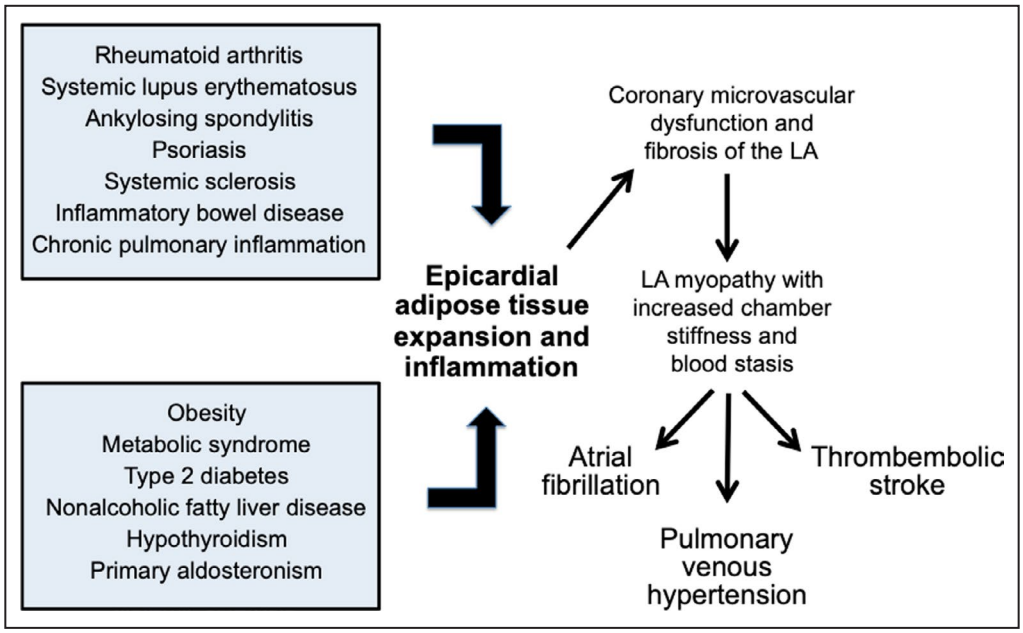

Figure 2. Chronic systemic inflammatory disorders and metabolic disorders that are linked to adipose tissue inflammation can lead to expansion of epicardial fat mass, which can cause a left atrial myopathy and its clinical consequences.
LA indicates left atrium.

adipogenesis and adipose tissue dysfunction (eg, hypothyroidism and primary hyperaldosteronism).[19,20] Each of these disorders is accompanied by a high prevalence of LA disease on non-invasive imaging, typically characterized by LA dilatation, fibrosis, or abnormal filling dynamics, and the severity of these abnormalities is often proportional to the magnitude of the metabolic derangement or systemic inflammation (Figure 2).[21–24]

This article refers to the LA myopathy in patients with a chronic systemic inflammatory disorder or with an adipogenic metabolic disease as "inflammation-related atrial myopathy", which can lead to "inflammation-related AF".

PATHOGENESIS AND IDENTIFICATION OF ATRIAL MYOPATHY IN STATES OF SYSTEMIC OR ADIPOSE TISSUE INFLAMMATION

Systemic inflammatory disorders can cause inflammatory injury to the coronary microcirculation, leading to microvascular dysfunction as well as myocardial fibrosis. Additionally, states of systemic or adipose tissue inflammation can evoke transformational changes in the adipose tissue within the epicardium, thereby expanding its mass and changing its biology into a proinflammatory state.[25] Since the epicardium and myocardium are connected through an unobstructed microcirculation, any biological derangement in epicardial fat is readily transmitted to the underlying myocardial tissues. Specifically, the secretion of proinflammatory adipocytokines (eg, tumor necrosis factor-α, interleukin 1-β, interleukin-6) from the dysfunctional epicardial fat depot can cause microcirculatory injury and fibrosis in the underlying adjoining myocardium, particularly the atrial myocardium. Epicardial adipose tissue expansion and inflammation are linked to the anatomical and pathophysiological substrates for AF in the adjoining atrial myocardium.[26,27]

Role of Proinflammatory Mediators in the Pathogenesis of LA Myopathy

These observations may explain several important findings. First, the chronic systemic inflammatory and metabolic disorders that have been linked to AF are all accompanied by an expansion of epicardial adipose tissue mass[28–35]; importantly, the increase in epicardial fat volume is proportional to the clinical severity of the disease and the intensity of systemic inflammation. Second, in patients with AF, there is a close association between the thickness and inflammatory state of epicardial fat and the severity of electrical abnormalities in the adjacent myocardium.[26,27] Third, epicardial fat volume predicts the incidence of AF in the community even in the absence of prior evidence of cardiovascular disease[36]; only the epicardial fat depot (and not other visceral fat) are associated with cardiac abnormalities[37]; and epicardial adipose tissue mass increases as AF evolves from a paroxysmal

to a persistent arrhythmia.[38] Fourth, there is a strong association between the mass of epicardial adipose tissue and derangements in coronary microvascular dysfunction and atrial geometry across a range of systemic inflammatory and metabolic disorders (Figures 1 and 2).[32,39,40]

The identity of the proinflammatory mediators released by epicardial adipose tissue depots that are responsible for injury to the adjoining atrial myocardium is unknown. However, 3 candidates (leptin, aldosterone, and natriuretic peptides) have been implicated in the pathogenesis of inflammation-related atrial myopathy and AF.[41] Increased activity of aldosterone and decreased activity of endogenous natriuretic peptides can promote epicardial adiposity and a transformation of its biology from a nutritive to a proinflammatory state.[42,43] Local increases in aldosterone can cause coronary microvascular injury and fibrosis[44]; these actions are normally opposed by those of endogenous natriuretic peptides,[45] but their influence may be minimized by increased clearance of natriuretic peptides by hypertrophied and inflamed adipocytes.[46] Finally, systemic inflammatory disorders and metabolic derangements linked to adipose tissue inflammation causes the release of leptin,[47,48] which can itself cause microvascular endothelial dysfunction and promote both inflammation and fibrosis.[49] Interestingly, there is a close relationship between both aldosterone and leptin with AF in experimental and clinical studies.[50,51]

CONSEQUENCES OF INFLAMMATION-RELATED ATRIAL MYOPATHY

The presence of an atrial myopathy can manifest itself clinically in 3 ways: (1) it can trigger atrial tachyarrhythmias; (2) it can increase pulmonary venous pressures and impair exercise tolerance; and (3) it can predispose to LA thrombus formation, systemic thromboembolism, and stroke (Figure 2).

Atrial Myopathy as a Cause of AF

The most clinically evident biomarker of the presence of an atrial myopathy is the finding of AF on the surface ECG. However, it seems likely that the atrial myopathy evolves for long periods of time before AF becomes clinically apparent, and it may exert clinically important effects even before they manifest AF.[52] Conversely, certain patients, especially those who have few inflammatory comorbidities (eg, those with low circulating levels of C-reactive protein), may have AF without the functional consequences of an underlying myopathy.[53–55]

For those with overt AF, it is difficult to ascertain to what extent the development and persistence of AF contributes to the progression of the atrial myopathy. Abolition of AF (ie, by catheter ablation) does not lead to predictably favorable benefits on LA structure and function.[56] Although LA size may decrease, this may be related to an inflammatory or fibrotic reaction within the chamber walls, since LA pressure frequently increases and LA systolic function decreases.[57–59] In patients who have a long-standing systemic inflammatory or metabolic disorder that is responsible for the atrial myopathy, the pathophysiological process in the atria is not necessarily resolved by the treatment of AF, and the injury produced by the ablation procedure can further impair the conduit, reservoir, and systolic functions of the left atrium.[60] Because of persistence of the abnormal inflammation-related atrial substrate, patients with increased epicardial adipose tissue volume[61]—eg, those with obesity, diabetes mellitus, metabolic syndrome, rheumatoid arthritis, and other proinflammatory states—are likely to experience AF recurrence following catheter ablation.[62–64] Patients with evidence of a meaningful atrial myopathy before the procedure (ie, LA dilatation and fibrosis) are unlikely to maintain sinus rhythm following ablation.[65,66] Although physicians might be tempted to perform repeat ablation procedures on these patients to control AF, these might add to the process of inflammation and fibrosis, resulting in a fibrotic and non-compliant left atriuim that becomes clinically manifest as severe pulmonary venous hypertension.[59,67] The risk of the “stiff LA syndrome” may be particularly high in those who have an underlying systemic inflammatory or metabolic disorder.[68]

Atrial Myopathy as a Cause of Pulmonary Venous Hypertension

The transmission of systemic or adipose tissue inflammation to the LA myocardium impairs its reservoir, conduit, and systolic functions. As a result, LA emptying decreases but the stiffness of the chamber increases, leading to disproportionately increased LA pressures, even if LA volumes are only modestly increased.[54] Although the inflammatory process that causes an atrial myopathy may also afflict the left atrium and impair its distensibility, the increase in LA pressures in patients with AF results primarily from the atrial myopathy and not because of the retrograde transmission of LV end-diastolic pressures to the left atrium. Whereas the pulmonary wedge pressure is typically lower than the LV end-diastolic pressure in patients in sinus rhythm, the opposite is true in patients with left heart disease and AF.[69] As a result, the LA myopathy can itself cause pulmonary venous hypertension that can promote exertional dyspnea and limit exercise tolerance.

Therefore, even in patients with AF who have evidence of associated abnormalities of LV filling, measurements of LA strain are more closely related to exercise capacity and outcomes than LV filling pressures.[70] Interestingly, the increase in LA pressures also appears to be more important for limiting functional capacity in patients with AF than exercise-induced tachycardia. Patients with AF with higher exercise-induced increases in heart rate do not show worse exercise capacity,[71] thus raising questions about the role of shortened diastole in limiting effort tolerance. Most importantly, in numerous double-masked randomized controlled trials, drug-induced rate control at rest or during exercise was accompanied by either no improvement or worsening of exercise tolerance, regardless of the pharmacological mechanism of action of the agent used to slow atrioventricular conduction.[72–75]

Atrial Myopathy as a Cause of Systemic Thromboembolism

Patients with a systemic inflammatory disorder that is linked to AF are at increased risk of thromboembolic stroke. For example, patients with rheumatoid arthritis and psoriasis have 50% to 100% increase in the risk of ischemic stroke, but the magnitude of the increased risk rises to 3-fold if afflicted individuals are aged <65 years.[76] Importantly, the increase in stroke risk greatly exceeds that predicted by the presence of traditional cardiovascular risk factors, but instead, parallels the clinical severity and duration of the arthritic disease and the intensity of systemic inflammation.[8,77] Similarly, the risk of stroke in AF-linked metabolic disorders (eg, metabolic syndrome or non-alcoholic fatty liver disease) is greater than can be accounted for by changes in blood pressure, serum cholesterol, or body weight, but appears to be closely linked to biomarkers of systemic inflammation (ie, C-reactive protein).[78,79]

So, is the increased risk of stroke in systemic inflammatory disorders related to the AF or to the underlying inflammation-related atrial myopathy? Physicians have long believed that the chaotic contraction of AF drives thrombus formation; however, it is the decreased flow velocity in the left atrium attributable to an underlying atrial myopathy that predisposes to thromboembolization, explaining why mitral regurgitation protects against the stasis of blood in the left atrium even though it increases the risk of AF by promoting LA dilatation.[80] The inflammatory and fibrotic process in the left atrium is a primary determinant of the impairment of the chamber's conduit functions, even in the absence of AF; in addition, inflammation and fibrosis may directly enhance the thrombogenicity of the atrial endocardium. Accordingly, atrial fibrosis predisposes to the occurrence of LA thrombus formation and stroke, independently of LA chamber size.[81]

Accordingly, the severity of the LA myopathy drives the risk of stroke and vascular brain injury in patients, with or without AF.[82,83] In patients who do not have risk factors that reflect the existence of an atrial myopathy, the risk of stroke in patients with AF is similar to that in patients without AF.[3] Conversely, CHA_2DS_2-VASc risk scores (which identify many patients with an atrial myopathy or who have epicardial adiposity[84]) predict the occurrence of stroke, even in patients without AF,[85] and in patients with high risk scores, the risk of thromboembolic events that is determined by the atrial myopathy is not increased further by the presence of AF.[86] It is noteworthy that among individuals with known AF, the rate of stroke in patients with rheumatoid arthritis and systemic lupus erythematosus is greater than can be explained by the CHA_2DS_2-VASc score,[87,88] presumably because the score does not incorporate measures of systemic inflammation or direct assessments of the atrial myopathy. Indeed, some have proposed that the CHA2DS2-VASc risk score be multiplied in patients who have a systemic inflammatory disorder.[89]

Doubts about the primacy of AF in causing stroke have been reinforced by the results of longitudinal studies that used continuous electrocardiographic monitoring devices to detect AF in patients at risk for or with a history of stroke. In these studies, at-risk patients generally did not exhibit evidence of AF in the month preceding the occurrence of stroke.[90,91] Patients who suffered a thromboembolic stroke manifested AF only rarely and transiently,[92] and in many patients, AF was observed only after the cerebrovascular event.[93] Importantly, the use of anticoagulants guided by the presence or absence of AF in individual patients at risk did not prevent thromboembolic events.[94]

Furthermore, pharmacological control or procedural abolition of AF has not been shown to reduce the risk of stroke in large-scale randomized controlled clinical trials. Randomized controlled trials that have compared rate-control and rhythm-control strategies in patients with established AF have demonstrated no reduction in the risk of systemic thromboembolism or stroke in patients assigned to rhythm control, even though these patients had a reduced burden of AF.[95] Paradoxically, the rhythm-control group experienced an increased risk of thromboembolic events,[96] possibly because oral anticoagulation was discontinued in some patients, based on the mistaken belief that AF (rather than the atrial myopathy) was the primary driver of stroke. Finally, abolition of AF by catheter ablation did not reduce the risk of stroke in a large-scale randomized controlled trial; in this study, oral anticoagulation therapy was maintained, although it was not likely to be in the therapeutic range in many patients.[97]

IDENTIFICATION OF PATIENTS WITH AN INFLAMMATION-RELATED ATRIAL MYOPATHY

How can patients with AF because of an inflammation-related atrial myopathy be identified in the clinical setting? Currently, a diagnosis of atrial myopathy can be discerned by advanced ECG signal processing, echocardiographic imaging of LA geometry, and magnetic resonance imaging of myocardial fibrosis. If these diagnostic modalities are not available, clues to the presence of an atrial myopathy can often be provided by 2 components of the commonly used CHA_2DS_2-VASc risk score—diabetes mellitus and heart failure. Diabetes mellitus represents a metabolic disorder that is accompanied by epicardial adiposity and adverse LA remodeling. Similarly, the presence of heart failure in patients with AF often represents the phenotype of heart failure with a preserved ejection fraction, a phenotype that is linked to systemic inflammation and an expansion of epicardial adipose tissue. However, in heart failure with a preserved ejection fraction, the inflammatory process in the epicardium is transmitted to the left ventricle (in addition of the left atrium), thereby impairing its ability to accommodate increases in blood volume without a disproportionate increase in filling pressures. The diagnosis of inflammation-related atrial myopathy may be further enhanced by the measurement of biomarkers of systemic inflammation (eg, elevated C-reactive protein). Furthermore, the predictive accuracy of risk scores for systemic thromboembolic events can be improved by incorporating information about abnormalities of LA geometry; such abnormalities identify patients at risk of stroke but would benefit from oral anticoagulation, even if they have low-risk CHA_2DS_2-VASc scores.[83,98–100]

CONCLUSIONS

AF has long been regarded as the consequence of hemodynamic stresses on the left side of the heart, particularly the pressure and volume overload states of hypertension and valvular heart disease. However, in recent years, AF has evolved into a disorder that is often a consequence of a broad range of systemic inflammatory or metabolic disorders, which can cause dysfunctional changes in adipose tissue depots, especially in the epicardium. The transmission of the proinflammatory state of an expanded epicardial adipose tissue mass to the adjoining myocardium is capable of producing adverse structural and functional changes in the left atrium, leading to the development of an atrial myopathy. The atrial myopathic process is characterized by coronary microvascular dysfunction, myocardial fibrosis, and an impairment of the chamber's conduit functions. It is most frequently manifest clinically as AF, and it can contribute (independently of the arrhythmia) to the development of pulmonary venous hypertension and thromboembolic stroke. Patients with an inflammation-related atrial myopathy may not respond well to rate or rhythm control strategies for AF, but anticoagulation is essential to reduce the risk of thromboembolic stroke.

ARTICLE INFORMATION

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Disclosures

Dr Packer has recently consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Johnson & Johnson, NovoNordisk, Pfizer, Sanofi, Synthetic Biologics, and Theravance. None of these relationships are relevant to the topic of this review.

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