

My atrial fibrillation is not your atrial fibrillation

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This editorial refers to ‘Clinical implication of an impaired fasting glucose and prehypertension related to new onset atrial fibrillation in a healthy Asian population without underlying disease: a nationwide cohort study in Korea’[†], by S.S. Lee *et al.*, on page 2599.

Atrial fibrillation (AF) is one of the major cardiovascular epidemics in the 21st century, causing ischaemic strokes, heart failure, cardiovascular deaths, and unplanned hospitalizations.¹ Even on optimal management, cardiac deaths and unplanned cardiovascular hospitalizations are common in AF patients. Current management of patients with AF does not differentiate greatly between patients with different pathophysiological forms of the disease.¹ While these therapies can prevent most strokes and improve quality of life, patients with AF are still at risk of cardiac deaths, often driven by heart failure or sudden death.^{1,2} The variable effect of interventions aimed at controlling rate, and especially at controlling rhythm, suggests that an understanding of the different drivers of AF in specific patient groups could help devise better strategies for prevention and management of the disease. Devising better concepts to prevent incident and recurrent AF seems essential to contain the adverse cardiovascular consequences of AF.

Cardiovascular risk factors have been well recognized to lead to the development and maintenance of atrial fibrillation. Recent studies have highlighted the marked structural and electrophysiological changes that occur within the atria in response to these risk factors, such as hypertension and obesity.³ Their role in the AF disease process has also been observed, with progression of the atrial myopathy even after successful ablation of AF. Indeed, even in individuals without established risk factors, there can be evidence of an atrial myopathy.⁴ Thus, other as yet unidentified factors apparently lead to AF in these persons.

It is in this context that the study by Lee and colleagues provides exciting insights.⁵ Using a nationwide data set of healthy Koreans, excluding those with established cardiovascular diseases known to contribute to AF, this study identified factors associated with the first manifestation of AF. A strength of the cohort is the standardized

acquisition of clinical data, including blood pressure and glucose tolerance, throughout this population as part of a National Health Check. Uniquely, the authors excluded patients with established [International Classification of Diseases (ICD)-coded] cardiovascular diseases known to increase AF risk, such as diabetes, established hypertension, heart failure, valvular heart disease, coronary artery disease, and others. Furthermore, patients with non-cardiac conditions that could be associated with AF, such as malignancy, pulmonary disease, or chronic rheumatoid diseases, were excluded. This can only be done in very large cohorts with a long follow-up as this eliminates a subpopulation with a high risk for incident AF. In this healthy Korean population, the authors found that elevated diastolic blood pressure and an impaired fasting glucose were associated with an increased risk of AF. In addition, they confirmed findings by others that a high body mass index (BMI) is associated with AF. Further exploration of the data showed that these factors added independently to AF risk in patients with low or normal BMI (<20 or 20–25), while the effect was much less clear in the part of the population that was obese.

Increasing age and BMI have been proposed as driving the increased prevalence and incidence of AF.² Experimental data suggest that electrical isolation of atrial cardiomyocytes by infiltrating fat cells, cross-talk between activated adipocytes and atrial myocardium, and abnormal secretory activity of atrial cardiomyocytes creates a substrate for AF in obese persons.^{3,6} Recent work has clearly established that reducing weight and treating the associated risk factors can reduce symptoms related to AF, reduce AF burden, and improve the maintenance of sinus rhythm—in some cases without the need for catheter ablation—in overweight and obese patients with AF.^{7,8}

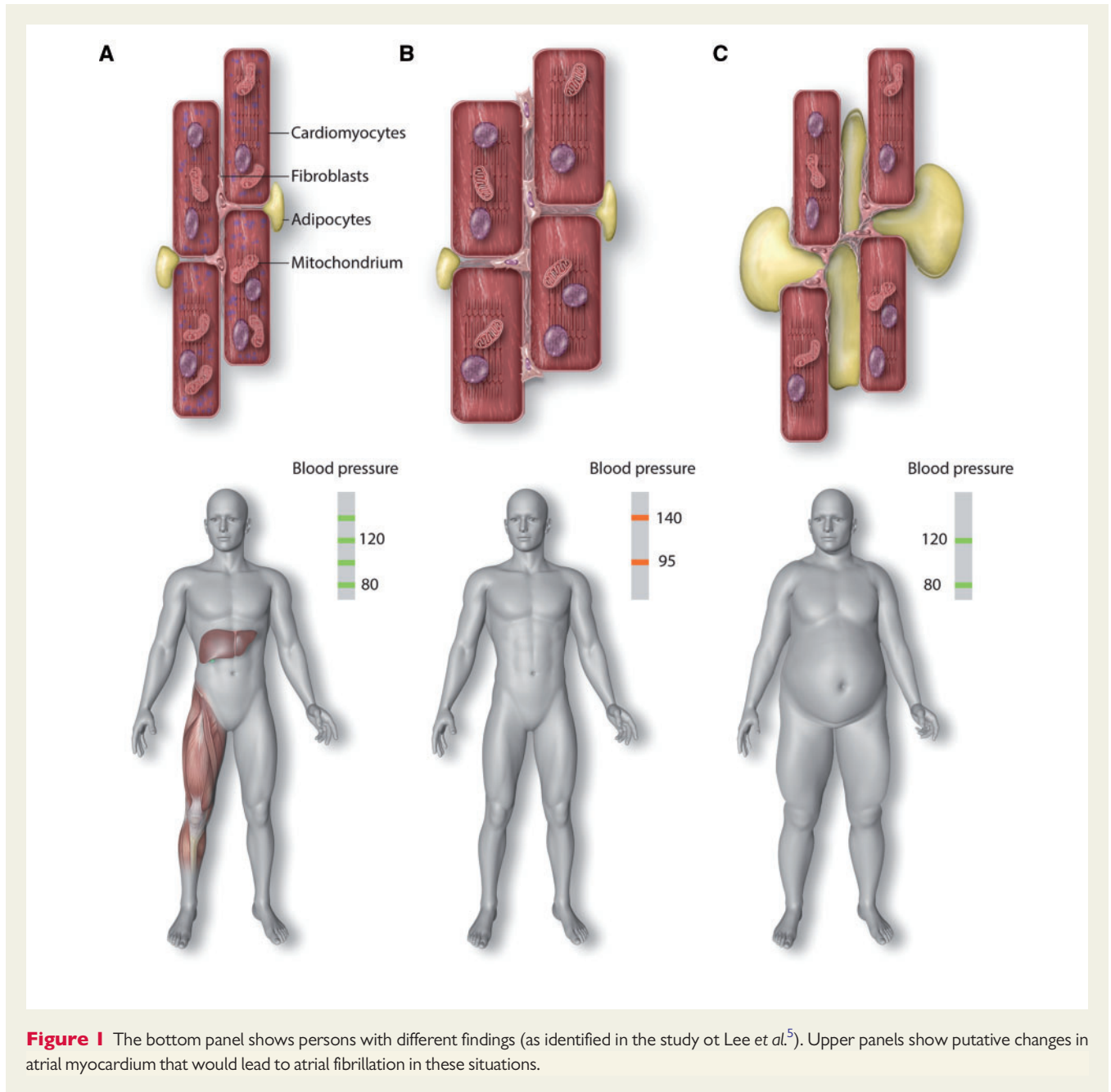
Hypertension remains the most common attributable risk for AF as a result of its prevalence within the community. Elevated blood pressure has been associated with slowing of atrial conduction due to formation of excessive extracellular matrix, and lowering of an elevated blood pressure has been suggested as an important intervention to prevent AF.⁹ The mechanisms that link elevated diastolic blood pressure to AF need further study, but they are probably related to increased wall pressure in the left atrium, structural changes in the atria, and activation of the renin–angiotensin–system

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and other fibrotic pathways. Interestingly, targeting blood pressure as an isolated risk factor in the clinic has yielded variable outcomes.¹⁰

The mechanism linking impaired fasting glucose to AF are less clear. It is well established that obesity, especially extreme obesity, contributes to increased cellular glucose tolerance and diabetes. The data presented here identify a role for impaired fasting glucose in patients of normal weight for AF risk, potentially pointing to the heritable components of pre-diabetes. Impaired fasting glucose will shift cellular metabolism, with potentially profound functional impacts in cells that require constant energy generation, such as cardiac cells, thus leading to increased metabolic stress in atrial myocardium. If the additive effects of increased diastolic blood pressure and impaired fasting glucose suggested by this analysis can be confirmed, one could

even speculate that AF is an early manifestation of increased atrial work load combined with suboptimal energy provision in the atria.

Common gene variants are strongly associated with AF,¹¹ including in Asian populations. Especially in young and otherwise healthy populations, heritable factors are expected to add to AF risk. It is therefore tempting to speculate that a genomic predisposition in the population studied by Lee *et al.* contributed to AF risk in interaction with an impaired fasting glucose or elevated diastolic blood pressure. *PITX2*, the gene that is closest to the strongest genomic variants associated with AF,^{11,12} controls genes regulating cellular metabolism^{13,14} and regulates the cardiac response to ischaemia,¹⁵ leading to distinct atrial electrophysiological changes including AF.¹⁶ Further translational studies are needed to characterize the interactions and regulatory

networks predisposing to AF when challenged with increased atrial pressure or altered cellular metabolism.

In addition to that mentioned above, other novel factors that require consideration include obstructive sleep apnoea, physical inactivity, alcohol excess, and increased aortic stiffness. What has become apparent is that it is important to undertake a meticulous evaluation for all culprit risk factors and to treat all potential risk factors in a given individual.¹⁷ Equally, the manner in which this intervention is delivered will be an important determinant of the implementation of change. There is a growing body of evidence to highlight the importance of an integrated patient-centric care to allow individualized and target-driven delivery of service to improve outcomes.^{1,17}

This elegant population-based analysis of healthy Korean subjects delineates distinct predisposing factors that lead to AF in different populations associated with obesity, elevated diastolic blood pressure, or impaired fasting glucose (Figure 1). This underpins the concept that different forms of AF will require different interventions for successful rhythm control management.¹⁸ Lee and colleagues underpin a role for weight loss in obese populations, and of blood pressure control in those with elevated diastolic blood pressures, and of restoring normal cellular glucose metabolism in the prevention of AF. Their study highlights the need to identify appropriate treatment targets for a given individual and potentially raises the possibility that these targets may differ based on the milieu of risk factors an individual harbours. Potentially, different patients with AF will benefit from different interventions to prevent recurrent AF, as already shown in obese AF patients. Thereby, this analysis proposes an avenue towards stratified rhythm control therapy in patients with AF as well as underpinning stratified prevention. In addition, the data call for research, e.g. into the mechanisms linking AF to impaired glucose tolerance in the absence of obesity.

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Conflict of interest: P.S. reports having served on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, Boston Scientific, and CathRx; having received lecture and/or consulting fees from Biosense-Webster, Medtronic, St Jude Medical, and Boston Scientific; and having received research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik, and Sorin. P.K. receives research support from the European Union, the British Heart Foundation, the Leducq Foundation, the Medical Research Council (UK), and the German Centre for Cardiovascular Research, from several drug and device companies active in atrial fibrillation, and has received honoraria from several such companies. He is listed as inventor on two patents held by the University of Birmingham (Atrial Fibrillation Therapy WO 2015140571, Markers for Atrial Fibrillation WO 2016012783).

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