Atrial Fibrillation in LVNC: Is it a distinct arrhythmia or a marker of disease?

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Left ventricular non-compaction (LVNC) is a cardiomyopathy characterised by prominent trabeculations and deep intertrabecular recesses, often leading to heart failure, thromboembolism, and sudden cardiac death. Atrial fibrillation (AF) frequently complicates LVNC, but its specific mechanisms and prognostic implications in this population remain a subject of ongoing clinical debate.

Understanding the interplay between LVNC and AF is critical for guiding management strategies, particularly regarding anticoagulation and rhythm control.1 The question persists: is AF a primary arrhythmia in LVNC, or merely a secondary manifestation of advanced myocardial disease?

KEY TAKEAWAYS

- The Pivot: AF in LVNC is more prevalent and carries a worse prognosis than in other cardiomyopathies, suggesting a distinct pathophysiological link.
- The Data: Patients with LVNC and AF have a significantly higher risk of thromboembolic events (HR 2.5; 95% CI, 1.8-3.4; PThe Action: Clinicians should maintain a high index of suspicion for AF in LVNC patients and consider early, aggressive anticoagulation, even in the absence of traditional risk factors.

Left ventricular non-compaction, a genetic cardiomyopathy, presents a unique challenge in cardiology due to its heterogeneous clinical manifestations and variable prognosis. The condition is defined by a two-layered myocardium, with a compacted epicardial layer and a non-compacted endocardial layer, often involving the left ventricle. This structural abnormality can lead to systolic and diastolic dysfunction, increasing the risk of arrhythmias and systemic embolisation. The prevalence of atrial fibrillation in patients with LVNC is notably higher than in the general population, and even higher than in other forms of cardiomyopathy, raising questions about a specific mechanistic link.1

Patients diagnosed with LVNC often present with symptoms ranging from asymptomatic to severe heart failure, ventricular arrhythmias, and systemic thromboembolism. The diagnosis typically relies on echocardiography, cardiac MRI, or cardiac CT, using established criteria that quantify the ratio of non-compacted to compacted myocardium. The mean age at diagnosis varies, but many patients are identified in adulthood, often after presenting with complications such as AF.2

The Distinct Pathophysiology of AF in LVNC

The increased susceptibility to atrial fibrillation in LVNC patients is not simply a consequence of ventricular dysfunction. Instead, it appears to stem from a combination of atrial structural remodelling, fibrosis, and electrical instability, exacerbated by the unique myocardial architecture of LVNC. The extensive trabeculations and intertrabecular recesses,

while primarily affecting the ventricles, contribute to a global cardiomyopathy that impacts atrial integrity.3
Histopathological studies reveal a higher incidence of atrial fibrosis in LVNC patients compared to age-matched controls with other cardiomyopathies. This fibrosis provides a substrate for re-entrant circuits, a common mechanism for AF initiation and perpetuation. The abnormal myocardial architecture also leads to increased wall stress and inflammation, further promoting atrial remodelling.4
Electrophysiological mapping studies in LVNC patients presenting with AF demonstrate prolonged atrial conduction times and increased dispersion of refractoriness. These electrical abnormalities create a highly arrhythmogenic environment, making AF more likely to occur and more difficult to manage. The left atrial appendage, often a source of thrombi in AF, also shows structural abnormalities in LVNC, contributing to the elevated thromboembolic risk.5

Clinical Outcomes and Thromboembolic Risk

Atrial fibrillation in patients with LVNC is not merely an incidental finding; it significantly worsens prognosis. Patients with LVNC who develop AF experience higher rates of heart failure exacerbation, stroke, and all-cause mortality. The risk of systemic thromboembolism is particularly elevated, even in patients with preserved left ventricular ejection fraction.6
A large retrospective cohort study, encompassing 1,200 patients with LVNC across 18 European centres, found that the incidence of AF was 28% over a median follow-up of 5.5 years. Patients with LVNC and AF had a significantly higher risk of thromboembolic events, including stroke and systemic embolism, compared to those with LVNC alone (HR 2.5; 95% CI, 1.8-3.4; P7
The study also reported a higher all-cause mortality in the AF group (HR 1.9; 95% CI, 1.4-2.6; P=.003). This suggests that AF acts as an independent prognostic marker in LVNC, rather than simply reflecting advanced disease. The median time to first thromboembolic event was 2.1 years in the AF group vs 4.8 years in the non-AF group.7

Anticoagulation Strategies and Rhythm Control

Given the heightened thromboembolic risk, anticoagulation is a critical component of managing AF in LVNC. Current guidelines for AF generally recommend anticoagulation based on CHA2DS2-VASc scores. But in LVNC, the presence of non-compaction itself, along with AF, may warrant a more aggressive approach. Some experts advocate for anticoagulation in all LVNC patients with AF, regardless of their CHA2DS2-VASc score, due to the unique thrombogenic substrate.8
Direct oral anticoagulants (DOACs) are generally preferred over vitamin K antagonists (VKAs) in AF patients due to their improved safety profile and ease of use. However, specific data on DOAC efficacy and safety in LVNC patients with AF are still emerging. The decision to initiate anticoagulation should involve a careful assessment of bleeding risk, which can be elevated in some LVNC patients due to co-morbidities.9
Rhythm control strategies, including antiarrhythmic drugs and catheter ablation, are often employed in AF management. But their efficacy in LVNC patients is less clear. The extensive atrial remodelling and fibrosis characteristic of LVNC can make AF more resistant to both pharmacological and interventional therapies. Catheter ablation success rates in LVNC patients with AF are reported to be lower than in patients with lone AF or AF associated with other cardiomyopathies, with recurrence rates as high as 40-50% at one year.10
Still, for symptomatic patients, rhythm control remains a viable option. The choice between rate and rhythm control should be individualised, considering the patient's symptoms, left ventricular function, and overall prognosis. For

clinicians managing these complex cases, a comprehensive resource like the Oxford Handbook of Cardiology can provide quick access to current best practices and diagnostic criteria.11

Where it Falls Short

The primary caveat in understanding AF in LVNC is the lack of large, prospective, randomised controlled trials specifically addressing this patient population. Most of the available data come from retrospective analyses and observational studies, which are prone to selection bias and confounding. The heterogeneity in diagnostic criteria for LVNC across studies also complicates generalisability. Furthermore, the optimal timing and type of anticoagulation, as well as the long-term efficacy of various rhythm control strategies, remain areas requiring further investigation. The trial was not powered to detect differences in specific LVNC genotypes, and that gap matters for personalised medicine.

Another limitation is the relatively small number of patients with LVNC compared to other cardiomyopathies, making large-scale trials challenging. Future research needs to focus on prospective registries and multicentre collaborations to gather more robust evidence. Genetic studies are also crucial to identify specific genetic mutations that predispose LVNC patients to AF, potentially allowing for earlier risk stratification and targeted interventions.12

The role of advanced imaging techniques, such as late gadolinium enhancement MRI, in predicting AF risk and guiding therapy in LVNC also warrants further exploration. Identifying patients at highest risk for AF and thromboembolism could lead to more proactive management strategies. The next trial needs to show whether early, aggressive rhythm control can alter the natural history of AF in LVNC, beyond merely symptom management.

CLINICAL IMPLICATIONS

The data on atrial fibrillation in left ventricular non-compaction underscore a critical need for heightened vigilance among clinicians. AF in these patients is not just another arrhythmia; it is a significant prognostic indicator that demands specific attention. Relying solely on conventional CHA2DS2-VASc scores for anticoagulation risk stratification in LVNC patients with AF is insufficient, given the unique thrombogenic substrate. Early and aggressive anticoagulation with DOACs should be the default, even in patients who might otherwise be considered low risk.

For cardiologists, this means a lower threshold for initiating anticoagulation and a more proactive approach to screening for AF in LVNC patients. Regular ECG monitoring and consideration of implantable loop recorders may be warranted, particularly in those with advanced LVNC or a family history of arrhythmias. The challenges with rhythm control therapies also highlight the need for realistic patient expectations and a focus on symptom management and stroke prevention.

The industry needs to recognise LVNC as a distinct entity in clinical trial design. Subgroup analyses in broader AF trials are rarely sufficient to address the specific pathophysiological mechanisms at play. Dedicated studies are essential to evaluate novel antiarrhythmic agents or ablation techniques tailored to the unique atrial remodelling seen in LVNC. Without this, patients with LVNC will continue to receive therapies based on evidence from populations with different disease characteristics.

Patients with LVNC and AF face a higher burden of disease and a greater risk of life-altering events like stroke. Clear communication about these risks and the rationale for aggressive anticoagulation is paramount. Empowering patients with knowledge about their condition and the importance of adherence to prescribed therapies can significantly improve outcomes, even when rhythm control proves elusive.

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