Recognizing Atrial Cardiomyopathy:

A Progressively Damaging Environment

ACT against Afib

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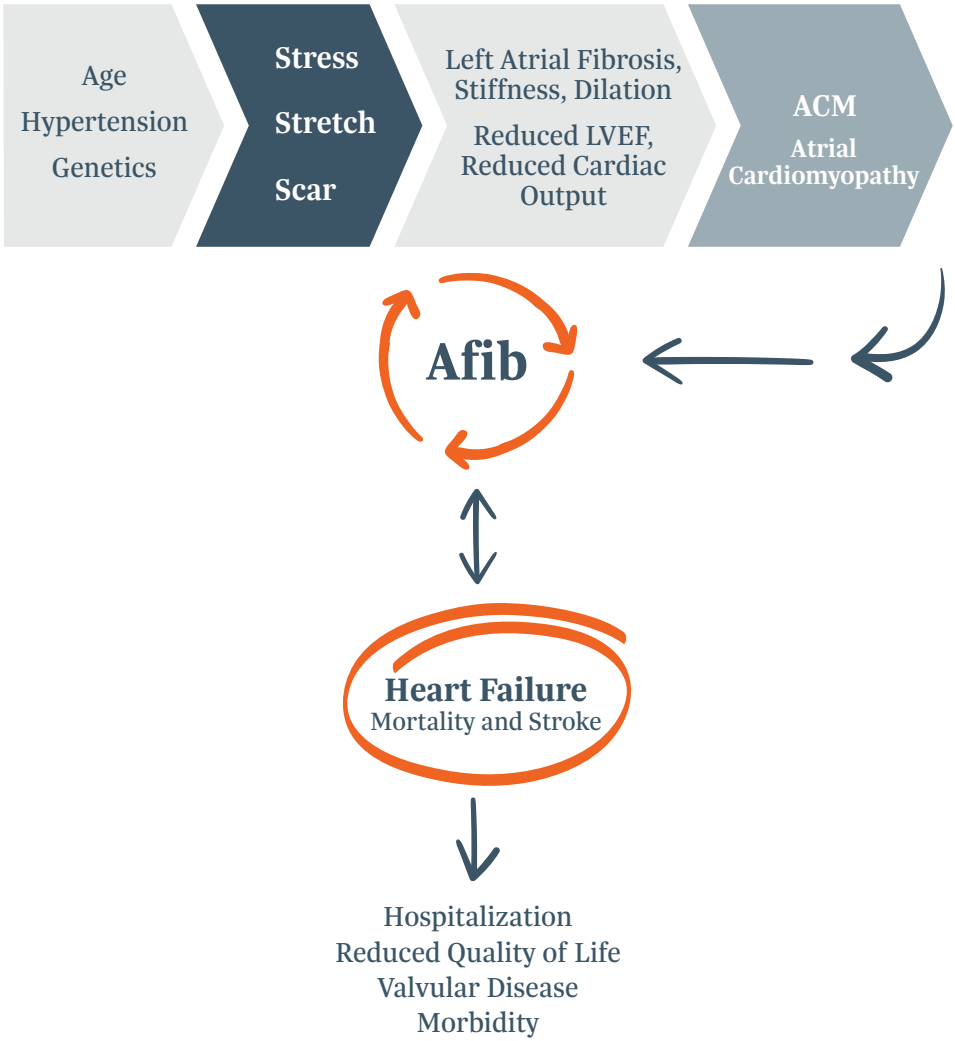
Structure, Rhythm, and Function All Play A Role In Cardiac Output



Why Is Atrial Cardiomyopathy Important?

Atrial cardiomyopathies are thought to precede the onset of atrial fibrillation (Afib), even in patients without gross structural or functional myocardial dysfunction.[1]

Most Afib patients have an established form of an atrial cardiomyopathy (ACM) which appears to be an important marker for the development of Afib in the future.[2]

ACM is a pathologic state that can increase the risk of developing Afib in the future.[2]

What Is Atrial Cardiomyopathy?

ACM is any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically-relevant manifestations.[3]

In short, ACM is atrial damage, which alters cellular structure or causes cell death.

Because atrial cells react quickly and extensively to pathological stimuli, they are susceptible to a broad range of genetic influences.[2]

ACM is the result of comorbidities such as hypertension, heart failure, and valvular disease, and has shown independent associations with stroke.[4]

EHRAS classification* of ACM:

1. Principal **cardiomyocyte** changes
2. Principally **fibrotic** changes
3. Combined **cardiomyocyte-pathology/fibrosis**
4. Primarily **non-collagen** infiltration

This simple classification can be useful to describe pathological changes in biopsies and to correlate results obtained from imaging tests with diseases.[3]

In the future this may help to define a tailored therapeutic approach in Afib.[2]

*EHRAS classes are not static and may vary over time, and therefore, the EHRAS classification is purely descriptive

Main Etiopathogenic Mechanisms Involved in Atrial Cardiomyopathy

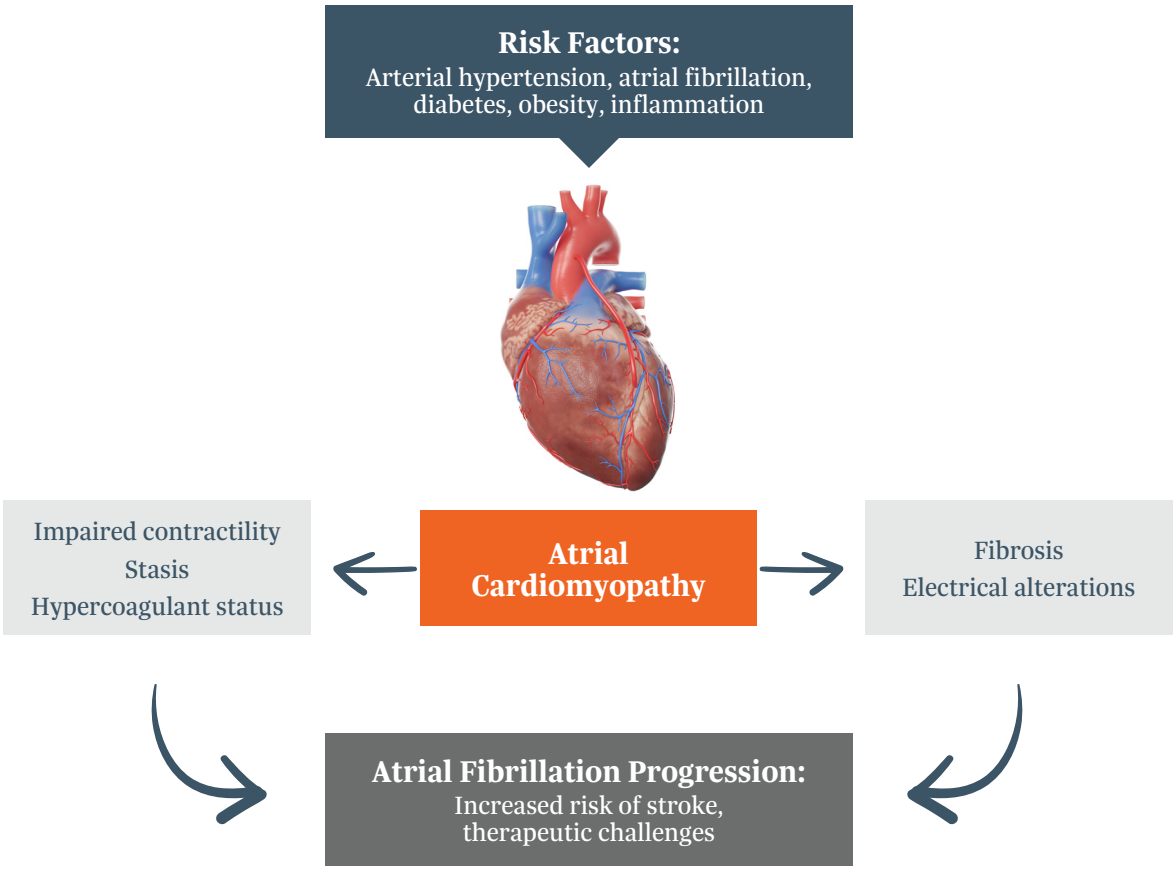


Figure 1

What Causes Atrial Cardiomyopathy?

The Environment: Cellular and Systemic

The Three S's

Stress

Proper cell function depends on a **delicate balance between antioxidants, reactive oxygen species (ROS) and antioxidant defense mechanisms.**

Oxidative stress occurs when that balance is persistently impacted, resulting in excessive ROS that damage components of cells, including mitochondria. This affects cell function and can lead to cell death. In addition, pressure overload on the heart that causes oxidative stress can be induced at the systemic level by cardiometabolic syndrome and generated at the cellular level by Afib.

Multiple Afib risk factors are closely associated with the formation of ROS, which is one of the main components of atrial remodeling.[2] Common causes of overworking and overload are smoking, high fat diet, hypertension, myocardial infarction (MI), persistent tachycardia, valvular pathology, obesity (any metabolic disorder), poor diet, excess alcohol, amphetamine use, chemotherapy, family history, and coronary artery disease. The 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation top 10 take-home messages highlight management of obesity, weight loss, physical activity, smoking cessation, alcohol moderation, hypertension, and other comorbidities.[19]

These risk factors generate the increased ROS that leads to the cellular changes resulting in inflammation and fibrosis.[2] Inflammation is an adaptive response that can be beneficial but becomes destructive when dysregulated.

Recent studies have shown that inflammation and excess ROS production seem to play a principal role in atrial remodeling. Even a mild systemic inflammation can be associated with increased cardiovascular risk, especially since proinflammatory status is found in numerous pathologies, such as hypertension, congestive heart failure (HF), coronary artery disease, obesity, or diabetes mellitus.[5]

Stretch

Anything that creates pressure or volume overload of the atria causes elongation of the cardiomyocytes, which results in increased atrial stretch.[6] As atrial size increases, so does the risk of stroke and persistent reentry circuits.

Changes that promote Afib and atrial remodeling – even before the first episode of Afib – occur in atria from patients with HF, hypertension, and mitral valve disease.[6]

Mechanical stretch of the heart, typically associated with pressure and/or volume overload, is believed to be an important contributor to the development of cardiac fibrosis. For example, left diastolic dysfunction or mitral valve disease can cause the left atrium to experience chronic sustained elevated pressure. Chronic stretch leads to left atrial dilatation, with heterogeneous remodeling of atrial architecture including myocyte hypertrophy, fibrosis, and gap junction remodeling.[7]

Scar

Another hallmark of structural remodeling and an important substrate of Afib is **fibrosis**, which is the formation of excessive extracellular matrix consisting of mainly fibroblasts and elastic and collagen fibers.[6]

Fibrosis and myocyte injury can result in scar tissue in the atrium, occurring when cell death comes into play.

In addition, **atrial inflammation is a key factor in the formation of fibrosis**.

A common cause of this is prolonged exposure to risk factors which promote fibrogenesis, such as hypertension, diabetes, ischemia, or congestive cardiac failure. Progressive fibrosis can lead to both conduction abnormalities and structural changes in the atrium.

Areas of scar are commonly located on the posterior atrial wall and around the pulmonary veins[8] and adjacent areas due to increased tension on pericardial reflections that anchor the posterior heart to the chest wall.

Left atrial scarring can serve as a substrate for slow conduction and intra-atrial reentry, and is associated with a lower ejection fraction, larger left atrium size, and increased inflammatory markers.[9]

Atrial Cardiomyopathy: How To Recognize It

There are three important mechanisms to detect the development of ACM:

- **Fibrosis**
- **Electrical dysfunction**
- **Mechanical dysfunction**[10]

Histological examination is only an option for few patients due to the invasive nature of a left atrial biopsy.[11]

Markers of ACM have been independently associated with incident stroke.[12]

Patients currently being enrolled in the LeAAPS trial have risk factors for Afib and ischemic stroke, which include the following ACM markers: elevated CHA_2DS_2-VASc score, Left Atrial Enlargement (LAE), and elevated NT-proBNP.

For more information on the LeAAPS trial, visit *clinicaltrials.gov*.

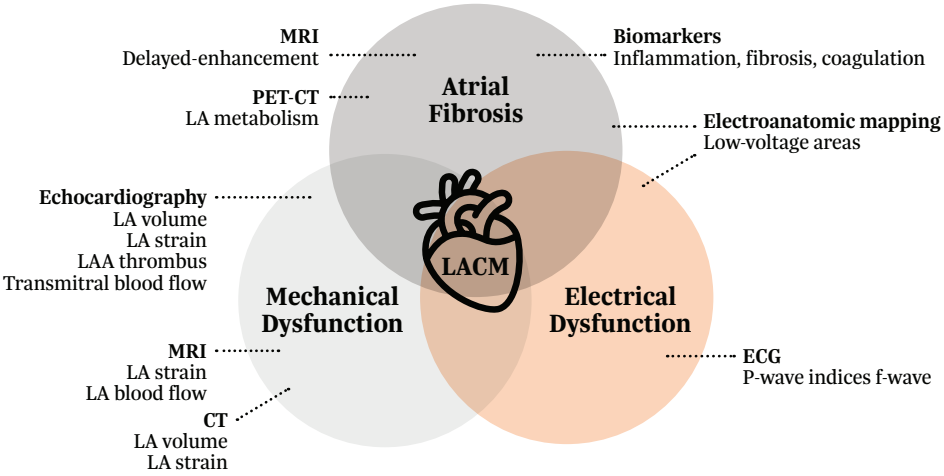


Figure 2 *Diagram of LACM as a composite entity of atrial fibrosis, mechanical dysfunction, and electrical dysfunction. Assessment of entities is achieved through different methods. CT, computed tomography; ECG, electrocardiology; f-wave, fibrillatory wave; LA, left atrial/left atrium; LAA, left atrial appendage; LACM, left atrial cardiomyopathy; MRI, magnetic resonance imaging; PET-CT, cardiac positron emission tomography - computed tomography.*

CHA_2DS_2-VASc

The CHA_2DS_2-VASc score is a point-based system used to stratify the risk of stroke in Afib patients and make recommendations for reducing risk.[13]

A higher number indicates a patient is more statistically likely to have stroke.

A higher score also predicts mortality in cardiac patients, and Afib recurrence.[14]

Clinical Predictors of Stroke Risk Associated with Afib

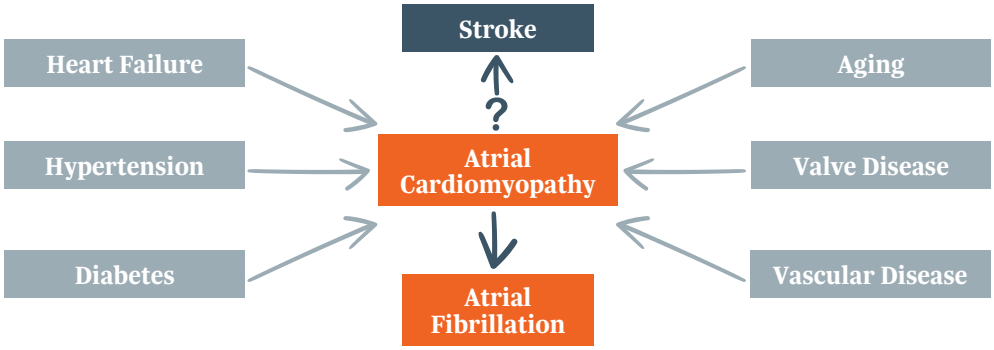


Figure 3 *Clinical Predictors of Stroke Risk Incorporated in the $CHADS_2$ and CHA_2DS_2-VASc Schemes All-Cause Atrial Cardiomyopathy*

This observation supports the idea that atrial cardiomyopathy may be a direct contributor to stroke risk. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischmic attack or thromboembolism.

	Condition	Points	CHA_2DS_2-VASc Score	Stroke Risk %
C	Congestive heart failure	1	0	0
H	Hypertension	1	1	1.3
A_2	Age ≥ 75 years	2	2	2.2
D	Diabetes mellitus	1	3	3.2
S_2	Prior Stroke or TIA or Thromboembolism	2	4	4.0
V	Vascular disease	1	5	6.7
A	Age 65-74 years	1	6	9.8
Sc	Sex category	1	7	9.6
			8	12.5
			9	15.2

CHA_2DS_2-VASc score = congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, age, sex category.

Figure 4 *CHA_2DS_2-VASc score and annual stroke risk.*

Left Atrial Enlargement (LAE)

Left atrial size and function have been increasing in importance to determining prognosis and risk stratification of patients.

In particular, LAE can result from an intrinsic atrial abnormality, altered workload, or compensation.

Atrial structural remodeling is characterized by increased interstitial fibrosis and by maladaptive structural changes secondary to inflammation, pressure, or volume overload.[5]

In a non-compliant left ventricle, the left atrium enlarges in order to maintain the left ventricle filling pressure, making LAE a marker of left ventricular diastolic dysfunction or increased filling volumes.[15] Additionally, LAE has been independently associated with an increased risk of ischemic stroke in the absence of Afib. Both LAE and Excessive Atrial Ectopy improved stroke risk prediction, which could impact stroke risk stratification, Afib screening, and stroke prevention before the onset of Afib.[4]

A meta-analysis of five prospective cohort studies indicates that LAE is associated with increased risk of stroke – and, for each increase of 1 cm in left atrial diameter, the odds of stroke were increased by 24%.[16]

NT-proBNP

The neurohormone B-type natriuretic peptide (BNP) is a regulator of cardiovascular function[17] and a biomarker used to measure cardiac function in the detection of HF.[18]

It's also a well-known indicator of congestive HF due to volume overload and myocardial damage and has shown a strong correlation with echocardiographic parameters of left atrial remodeling and dysfunction.[11]

Bringing It All Together

Death, longevity, and the environment for Afib

In short, ACM is a sick atrium, developing and exhibiting all the characteristics of Afib – even before Afib exists.

In addition to creating the environment that can lead to the development of Afib, the markers for ACM are independently associated with increased risk of stroke.[1]

NOTES

Figure 1 adopted from Dmour, B.A. et al. (2021). Latest insights into mechanisms behind atrial cardiomyopathy: It is not always about ventricular function. Diagnostics, 11(3):449.

Figure 2 adopted from Kreimer, F. & Gotzmann, M. (2022). Left Atrial Cardiomyopathy – A Challenging Diagnosis. Front. Cardiovasc. Med, 9:942385. doi: 10.3389/fcvm.2022.942385.

Figure 3 adopted from Guichard, J.B. & Nattel, S. (2017). Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad?. Journal of the American College of Cardiology, 70(6):756-65.

Figure 4 adopted from Gažová, A. et al. (2019). Predictive value of CHA_2DS_2-VASc scores regarding the risk of stroke and all-cause mortality in patients with atrial fibrillation (CONSORT compliant). Medicine, 98(31):e16560. https://doi.org/10.1097/MD.0000000000016560.

Figure 5 adopted from Avan, A. et al. (2019). Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. BMC medicine, 17(1):1-30.

Figure 6 adopted from Patton, K.K. et al. (2009). N-terminal pro-B-type natriuretic peptide is a major predictor of the development of atrial fibrillation: the Cardiovascular Health Study. Circulation, 120(18):1768-74.

Figure 7 adopted from Kiviniemi, T. et al. (2019). Performance of CHA_2DS_2-VASc score for stroke prediction after surgical aortic valve replacement. The Journal of Thoracic and Cardiovascular Surgery, 157(3):896-904.

Figure 8 adopted from Yaghi, S. et al. (2015). Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke, 46(6):1488-93.

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