

# Risk Factors for Death in Patients with Atrial Fibrillation

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**Abstract:** With the aging society and increasing risk factors for cardiovascular diseases, the incidence of atrial fibrillation is gradually increasing, seriously affecting human health. Previous studies have shown that hypertension, diabetes, heart failure, chronic kidney disease, etc, increase the risk of death of patients with atrial fibrillation. Research has shown that cardiac pathological remodeling is the fundamental pathophysiological mechanism for atrial fibrillation, which is closely related to thromboembolism and death in patients with atrial fibrillation. At present, there is limited research on the risk factors for increased mortality in patients with atrial fibrillation. Therefore, this article will review the related factors that increase the risk of death in patients with atrial fibrillation.

**Keywords:** Atrial Fibrillation; Death; Risk Factors

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## Introduction

Atrial fibrillation (AF) is a common supraventricular arrhythmia, characterized by abnormal atrial electrical stimulation and systolic dysfunction. It can lead to cardiac dysfunction. AF not only reduces the quality of life of patients, but also increases the all-cause mortality rate of patients with metabolic cardiovascular disease by 1.5-1.9 times<sup>[1,2]</sup>. The ion channels of myocardial cells alter the excitability of atrial muscles, forming a reentrant loop, leading to the occurrence of AF, activating the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS), promoting myocardial fibrosis, and leading to cardiac pathological remodeling and dysfunction<sup>[3]</sup>. Research has shown that AF is closely related to adverse outcomes such as thromboembolism and increased mortality<sup>[4,5]</sup>. Currently, there is relatively little research on the risk factors for increased mortality in patients with AF, so this article provides a review of this research.

## 1. Atrial fibrillation and death

The study found that the incidence rate of ischemic stroke in patients with AF was higher and more serious, the cerebrovascular mortality increased<sup>[6]</sup>. AF can lead to hemodynamic abnormalities, cardiac endothelial dysfunction, platelet aggregation, and coagulation factor release, promote left atrial thrombosis, and increase the incidence rate of thromboembolic stroke<sup>[7]</sup>. Toshimi et al<sup>[8]</sup> found that without cardiovascular risk factors, AF is also an independent risk factor for stroke related death. In addition, research has confirmed that with the use of oral anticoagulants, the cerebrovascular mortality rate in patients with AF has decreased, but there is still a higher risk of cardiovascular death<sup>[9]</sup>. Especially among the elderly, there is a significant increase in cardiovascular mortality<sup>[10]</sup>. The mechanism of increased mortality in patients with AF is closely related to the pathological remodeling of the heart caused by various cardiovascular diseases and fatal arrhythmias caused by cardiac dysfunction<sup>[4,11]</sup>.

## 2. The death risk factors of AF

### 2.1 Women

Research has found that elderly female with AF have a higher risk of thromboembolism related stroke, and have a higher all-cause mortality rate<sup>[1,12]</sup>. Women with AF have a 2.5 times higher cardiovascular mortality rate than men<sup>[13]</sup>. In a meta-analysis of 30 studies, it was found that female AF patients had an all-cause mortality rate 12% higher than male<sup>[14]</sup>. At present, there is no mechanism to clearly explain the gender differences in AF mortality, which may be related to insufficient treatment in female AF patients, differences in anticoagulant drug responsiveness, and a high risk of fatal adverse events caused by antiarrhythmic drugs<sup>[15,16]</sup>.

## 2.2 Smoking

Smoking is a risk factor for AF, and research has confirmed that smoking is associated with a high risk of thromboembolism and death in AF patients<sup>[17]</sup>. Kwon et al.<sup>[18]</sup> found that AF patients who smoke are more prone to ischemic stroke and cardiovascular death. Lee et al.<sup>[19]</sup> found through follow-up of newly diagnosed patients with AF that patients who did not quit smoking had a significantly higher risk of cerebrovascular death compared to those who quit smoking. Alanna M Chamberlain et al.<sup>[20]</sup> also found that smokers with AF have a higher risk of all cause death compared to non-smokers. Smoking can increase the risk of death in patients with AF by promoting catecholamine secretion, increasing cardiac contraction, leading to myocardial ischemia. It can also be affecting blood lipids, promoting oxidative stress response, damaging vascular endothelial function, accelerating atherosclerosis, increasing the risk of myocardial infarction and heart failure<sup>[17]</sup>.

## 2.3 Obesity

Obesity can lead to the transition from paroxysmal to persistent AF<sup>[21]</sup>. Obese patients often have an increase in epicardial adipose tissue. Currently, research has found that epicardial adipose tissue has metabolic activity, which can induce myocardial fibrosis and cardiac dysfunction<sup>[22]</sup>. It was found that obesity can prolong the QT gap and increase the risk of sudden cardiac death<sup>[23]</sup>. However, the impact of obesity on the mortality of AF patients is controversial. Research has found that high body mass index (BMI) is the main risk factor for death in patients with AF<sup>[24]</sup>. However, some studies have found a reverse relationship between BMI and mortality in patients with AF. Compared with patients with normal BMI, low-weight patients have higher all-cause mortality, while overweight and obese patients have lower all-cause mortality<sup>[25]</sup>. The “obesity paradox” has also appeared in recent studies. When BMI is less than 30kg/m<sup>2</sup>, all-cause mortality is negatively correlated with BMI<sup>[26]</sup>. This may be related to the fact that patients with higher BMI are often younger, with fewer comorbidities, and that rhythm control and anticoagulant therapy are more commonly used in patients with AF in higher BMI.

## 2.4 Inflammation

Inflammation plays an important role in the progression of cardiovascular diseases, and participate in cardiac remodeling, leading to the persistence of AF<sup>[27]</sup>. Inflammation is an important response for the body's immune defense, but sustained or inappropriate inflammation can also cause damage to the body. Research has confirmed that inflammation can increase the risk of death in AF patients. Aulin et al.<sup>[28]</sup> found that the levels of interleukin-6 are positively correlated with all-cause mortality in AF patients. Hermida et al. confirmed that high levels of hypersensitive C-reactive protein are independent risk factors for all cause and cardiovascular death in AF patients<sup>[29]</sup>. Some studies have also found that AF patients have a higher proportion of CD4+CD28- T cells compared to non-atrial fibrillation patients, and CD4+CD28- T cells are significantly correlated with cardiovascular mortality in AF patients<sup>[30]</sup>. Inflammation can increase the risk of thromboembolism in AF patients, leading to cerebrovascular mortality. It is related to the hypercoagulable state, platelet activation, and endothelial dysfunction. Inflammation can also promote cardiac remodeling and increase cardiovascular mortality in AF patients<sup>[31, 32]</sup>.

## 2.5 Hypertension

Research has confirmed that hypertension is the risk factor of AF<sup>[33]</sup>. In addition, studies have also confirmed that hypertension can increase the risk of death in AF patients. Wang Jianping et al.<sup>[34]</sup> found that hypertension above grade 2 is a high-risk factor for all-cause mortality in non-valvular atrial fibrillation patients. G A Dan et al.<sup>[35]</sup> also found that when AF and hypertension coexist, the all-cause mortality rate is higher than in patients with AF alone. The activation of the RAAS, inflammation, and oxidative stress in the long-term hypertensive state of the body can lead to myocardial fibrosis and ischemia, which can lead to the occurrence of arrhythmias, increase the risk of ventricular arrhythmias in AF patients, and increase the risk of sudden cardiac death<sup>[33]</sup>. Moreover, the increase in left ventricular volume load caused by hypertension can develop into hypertensive heart disease and congestive heart failure, leading to a significant increase in cardiogenic death in AF patients.

## 2.6 Chronic kidney disease

Chronic kidney disease (CKD) often coexists with AF, leading to an increased all-cause mortality rate in AF patients<sup>[36,37]</sup>. Research has confirmed that CKD can increase the risk of thromboembolic events in AF patients by affecting coagulation function, leading to an increased risk of cerebrovascular death<sup>[37]</sup>. Research has found that in AF patients, as the glomerular filtration rate decreases, all-cause and cardiovascular mortality rates are increased<sup>[38]</sup>. The hemodynamic changes in the heart caused by AF can promote the development of end-stage kidney disease by reducing renal perfusion<sup>[39]</sup>. In addition, AF can further damage renal function through increasing fibrosis in myocardial and renal tissues, upregulation of fibrinogen, and renal micro thrombosis formation<sup>[40]</sup>. The disorder of calcium and phosphorus metabolism, vascular calcification caused by CKD, and the decrease in coronary blood flow caused by AF can lead to insufficient coronary blood supply, myocardial ischemia, increasing risk of coronary heart disease and susceptibility to acute myocardial infarction and sudden cardiac death. In summary, the correlation between AF and CKD promotes a significant increase in the risk of death.

## 2.7 Diabetes

Diabetes is one of the risk factors of AF. Many studies have confirmed that the death of AF patients with diabetes is significantly increased. Polovina et al.<sup>[41]</sup> found through a median 5-year follow-up of 1803 AF patients with T2DM, the all-cause mortality rate was 56% higher than that of non T2DM AF patients, and the cardiovascular mortality rate was 48% higher. Karayiannides S et al.<sup>[42]</sup> found that the effect of diabetes and AF increased the all-cause mortality rate by twice compared with the general population. A recent meta-analysis of 21 studies confirmed that diabetes is associated with a higher risk of cardiovascular and all-cause death in AF patients<sup>[43]</sup>. The mechanism of the impact of diabetes on the survival of AF patients has not been completely clear, and the following reasons are mainly considered. First, insulin resistance exists in patients with diabetes, which leads to abnormal lipid metabolism of myocardial cells, leading to heart “lip toxicity”; Secondly, diabetes can lead to cardiac electrical, structural and autonomic nerve remodeling, make AF recur and continue, and affect the stability of hemodynamics; Third, diabetes can promote the development of cardiomyopathy and heart failure through systemic inflammation, microvascular dysfunction and oxidative stress, and increase the risk of cardiovascular death<sup>[23,42,44]</sup>.

## 2.8 Heart failure

Heart failure (HF) and AF often occur together, promoting each other and leading to poor prognosis. Cardiovascular death of AF is closely related to HF. Marijon et al.<sup>[45]</sup> followed up 18113 AF patients for a median of 2 years and found that cardiovascular death accounted for 37.4% of the total deaths, HF being the strongest predictor of cardiovascular death. In Framingham’s study, it was found that AF patients with HF have an increased risk of all-cause death<sup>[46]</sup>. In another study, it was found that HF is the main death cause after one year of new onset AF<sup>[47]</sup>. AF is mainly characterized by irregular contraction of the atrium. Changes in the excitation contraction coupling of myocardial cells and myocardial fibrosis can lead to abnormal atrioventricular node conduction, leading to an increase in the occurrence of ventricular arrhythmias. In AF patients with HF, cardiac remodeling is more significant, and the stress between myocardial cells also undergoes significant changes. Under the influence of ventricular arrhythmias, sudden cardiac death is more likely to occur<sup>[11,48]</sup>. HF is often accompanied by various diseases such as diabetes, hypertension, metabolic syndrome, renal insufficiency, etc. In patients with AF and HF, the above diseases are also often accompanied. The combined effect of these diseases significantly increases the all-cause mortality of patients with AF<sup>[49]</sup>.

## 3. Summary

AF as a common arrhythmia in clinical practice, can seriously affect the quality of life of patients and significantly increase the risk of death. Studies have found that many factors are closely related to the death of patients with AF, including women, smoking, obesity, inflammation, hypertension, diabetes, CKD, HF, etc. Clarifying the impact of various factors on the death of AF patients is of great significance for their diagnosis and treatment. According to the impact of risk factors on the death of AF patients, risk stratification management can be carried out for the prognosis of AF patients, and active prevention and treatment of risk factors may reduce the death of AF patients. Currently,

research has shown that the impact of certain factors such as gender and obesity on mortality in AF patients is still controversial, and further clinical research is needed to clarify.

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