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# Current evidence of gut microbiota dysbiosis and its role in atrial fibrillation and cardiovascular diseases

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**Abstract:** The human gut microbiota has emerged recently as an important regulator of cardiovascular physiology through its effects on metabolism, immune signaling, and systemic inflammation. Increasing evidence suggests that alterations in intestinal microbial composition (dysbiosis) may contribute to the development and progression of atrial fibrillation (AF). This review summarizes current evidence on gut microbiota alterations, microbiota-derived metabolites, and their mechanistic links to atrial fibrillation pathogenesis and potential therapeutic strategies. Patients with AF demonstrate reduced microbial diversity and characteristic shifts in bacterial taxa, including depletion of short-chain fatty acid–producing bacteria and enrichment of potentially pro-inflammatory microorganisms. Gut microbiota–derived metabolites appear to play a key role in mediating these effects. Trimethylamine N-oxide (TMAO), lipopolysaccharide (LPS), and phenylacetylglutamine (PAGln) promote oxidative stress, endothelial dysfunction, and activation of inflammatory pathways such as NF-κB and the NLRP3 inflammasome, leading to atrial fibrosis, electrical remodeling, and increased arrhythmogenic susceptibility. In contrast, short-chain fatty acids exert anti-inflammatory and cardioprotective effects that may stabilize cardiac electrophysiology. Importantly, the relationship between gut microbiota and atrial fibrillation appears to be bidirectional, as cardiovascular disease itself may influence intestinal barrier integrity and microbial composition. Understanding the gut–heart axis may open new perspectives for risk stratification and therapeutic strategies, including dietary interventions and microbiome-targeted therapies. Further clinical studies are required to determine whether modulation of the gut microbiota can effectively prevent or modify the course of atrial fibrillation.

**Keywords:** atrial fibrillation, gut microbiota, gut–heart axis, dysbiosis, microbiota-derived metabolites, inflammation.

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## Introduction

The human gut microbiota constitutes a complex microbial ecosystem that plays a fundamental role in host metabolism, immune regulation, and maintenance of intestinal barrier integrity. Increasing evidence indicates that intestinal microorganisms influence not only gastrointestinal physiology but also systemic processes, including inflammation, metabolic homeostasis, and cardiovascular function. [1, 2, 3] This concept has led to the emergence of the gut–heart axis, which describes potential bidirectional interactions between the intestinal microbiome and the cardiovascular system.

Dysbiosis, defined as a disruption of microbial composition characterized by reduced diversity and expansion of pro-inflammatory taxa, has been recently associated with cardiometabolic disorders such as hypertension, coronary artery disease, heart failure, and atrial fibrillation (AF). [1, 2, 3, 4] Several mechanisms have been proposed to explain this association, including systemic inflammation, oxidative stress, metabolic disturbances, and autonomic nervous system modulation. [1, 3, 4, 5, 6]

Atrial fibrillation, the most common sustained cardiac arrhythmia worldwide, remains a major cause of stroke, heart failure, and cardiovascular mortality. While classical mechanisms of AF pathogenesis include atrial fibrosis, electrical remodeling, and autonomic dysregulation, accumulating evidence suggests that systemic metabolic and inflammatory pathways may also contribute to arrhythmogenesis. In this context, alterations in gut microbiota composition have recently emerged as a potential contributor to AF development and its progression. [1, 3, 5]

Clinical studies have demonstrated distinct microbial signatures in patients with AF, including reduced microbial α-diversity and depletion of short-chain fatty acid (SCFA)–producing bacteria such as *Faecalibacterium*, *Alistipes*, and *Bifidobacterium*, accompanied by enrichment of potentially pathogenic taxa including *Ruminococcus*, *Streptococcus*, and *Enterococcus.* [1, 5, 7] These changes may promote intestinal barrier dysfunction and systemic translocation of microbial components, thereby triggering inflammatory signaling pathways involved in atrial structural and electrical tissue remodeling.

Microbiota-derived metabolites, including trimethylamine N-oxide (TMAO), lipopolysaccharide (LPS), and phenylacetylglutamine (PAGln), have been implicated in endothelial dysfunction, inflammation, and myocardial fibrosis, whereas short-chain fatty acids exert protective anti-inflammatory effects. [1, 2, 3] Despite growing interest in this field, the mechanistic links between gut microbiota alterations and cardiac arrhythmogenesis remain incompletely understood.

Therefore, this review summarizes current evidence regarding gut microbiota dysbiosis, microbiota-derived metabolites, and their potential role in the pathogenesis of atrial fibrillation.

## Gut microbiota alterations in atrial fibrillation

### *Microbial diversity and global dysbiosis*

The human gut microbiota is dominated by bacteria belonging primarily to the Firmicutes and Bacteroidetes phyla, which together account for the majority of microbial species in healthy individuals. A balanced microbial composition is essential for maintaining metabolic homeostasis, immune regulation, and intestinal barrier integrity. In contrast microbial imbalance has been increasingly associated with cardiometabolic diseases, including atrial fibrillation (AF). [1, 2, 3, 4]

Several clinical studies have demonstrated that patients with AF exhibit reduced gut microbial diversity, a hallmark feature of dysbiosis. Lower α-diversity is generally considered an indicator of impaired microbial ecosystem stability and has been associated with increased systemic inflammation and metabolic dysfunction. [1, 5, 7] In addition to reduced diversity, AF-related dysbiosis is characterized by alterations in the relative abundance of specific bacterial taxa and shifts in the overall microbial community structure.

One of the commonly reported features of dysbiosis in cardiovascular disease is an altered Firmicutes-to-Bacteroidetes (F/B) ratio, which has been associated with metabolic disturbances and systemic inflammatory responses. Although the exact significance of this ratio remains debated, changes in the F/B balance may reflect broader microbial ecosystem disruption contributing to cardiometabolic pathology. [6, 8]

### *Specific taxonomic changes in AF*

Beyond global changes in microbial diversity, several studies have identified distinct microbial signatures associated with atrial fibrillation. These alterations include both depletion of beneficial commensal bacteria and enrichment of potentially pathogenic taxa.

In particular, AF has been associated with reduced abundance of short-chain fatty acid (SCFA)-producing bacteria, including genera such as *Faecalibacterium*, *Alistipes*, and Bifidobacterium. These microorganisms are key producers of short-chain fatty acids (SCFAs), which play an important role in maintaining intestinal and systemic homeostasis (Fig. 1). Their depletion may therefore contribute to increased intestinal permeability and systemic inflammatory activation. [1, 5, 7]

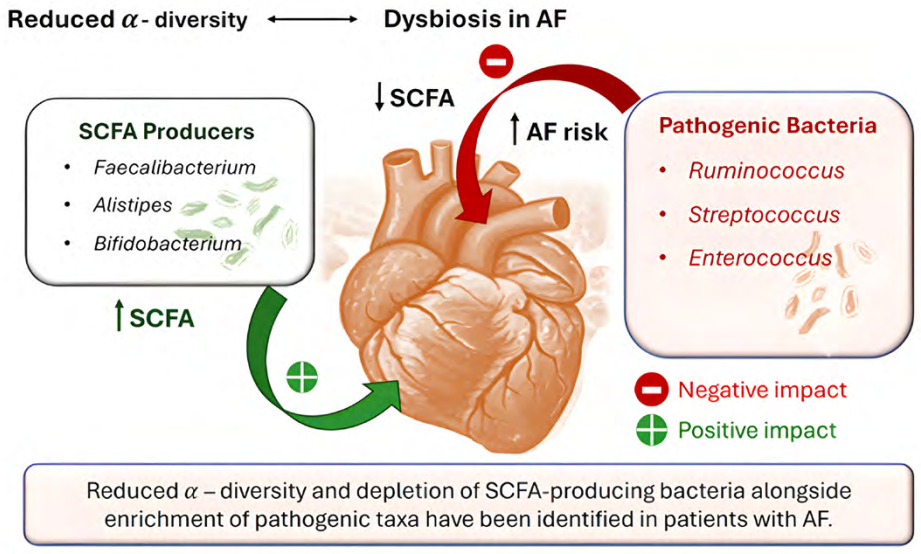


**Fig. 1.** Microbial signatures associated with atrial fibrillation. Schematic overview of gut microbiota alterations associated with atrial fibrillation, including reduced microbial diversity, depletion of SCFA-producing bacteria, and enrichment of potentially pathogenic taxa.

Conversely, enrichment of potentially pro-inflammatory or opportunistic taxa has been observed in patients with AF. These include genera such as *Ruminococcus*, *Streptococcus*, and *Enterococcus*, which have been associated with inflammatory signaling, altered host metabolism, and increased production of microbial metabolites involved in cardiovascular pathology (Fig. 1). [1, 5, 7]

Some studies have also reported increased abundance of trimethylamine (TMA)-producing bacteria, including *Prevotella* and *Bacteroides*. These taxa are of particular interest because TMA serves as a precursor of trimethylamine N-oxide (TMAO), a gut microbiota–derived metabolite implicated in cardiovascular disease and arrhythmogenesis. [6, 8]

### *Microbiota alterations and AF phenotype*

Emerging evidence suggests that the degree of gut microbiota dysbiosis may correlate with clinical characteristics and duration of atrial fibrillation. For example, patients with persistent or long-standing AF appear to exhibit more pronounced alterations in gut microbial composition compared with individuals with paroxysmal AF. [6, 9]

This observation supports the hypothesis that sustained atrial remodeling and systemic inflammatory activation may interact with microbial dysbiosis in a self-reinforcing pathological cycle. Chronic AF may lead to hemodynamic disturbances, intestinal hypoperfusion, and congestion, which in turn can impair intestinal barrier function and promote microbial imbalance. [3, 9]

Additionally, gut microbiota composition in patients with AF may be influenced by several confounding factors frequently present in this population, including age, metabolic syndrome, obesity, diabetes, medication use, and dietary patterns. These factors may further complicate the interpretation of microbiome studies and highlight the need for carefully designed longitudinal investigations. [3, 6]

### *Clinical evidence linking gut dysbiosis and AF*

Multiple observational studies have provided evidence supporting an association between gut microbiota alterations and atrial fibrillation. For example, population-based analyses have demonstrated that specific microbial genera are independently associated with incident AF, suggesting that gut microbiome composition may serve as a potential biomarker for arrhythmia risk. [2]

Furthermore, alterations in microbial metabolic profiles have been reported in patients with AF, including increased production of metabolites linked to inflammation, thrombosis, and myocardial remodeling. These findings support the concept that gut microbiota alterations may contribute not only to AF development but also to disease progression and recurrence after therapeutic interventions such as catheter ablation. [6, 10, 11]

Despite these consistent associations, most available evidence derives from observational human studies and experimental animal models, and a direct causal relationship between gut dysbiosis and atrial fibrillation has not yet been definitively established. Further prospective studies and mechanistic investigations are therefore required to clarify the clinical significance of gut microbiota alterations in AF pathophysiology.

## Microbiota-derived metabolites in atrial fibrillation

Gut microbiota influences cardiovascular physiology not only through alterations in microbial composition but also through the production of bioactive metabolites that interact with host metabolic, inflammatory, and neurohumoral pathways. Increasing evidence suggests that these microbiota-derived metabolites play a central role in linking intestinal dysbiosis with cardiovascular diseases, including atrial fibrillation (AF). Several compounds generated by microbial metabolism have been implicated in arrhythmogenesis through their effects on inflammation, oxidative stress, endothelial function, autonomic regulation, and myocardial structural remodeling. [1, 2, 3, 6]

Among the most extensively studied metabolites associated with AF are trimethylamine N-oxide (TMAO), lipopolysaccharide (LPS), phenylacetylglutamine (PAGln), bile acids, and short-chain fatty acids (SCFAs). While some of these metabolites exert pro-inflammatory and proarrhythmic effects, others appear to play protective roles in maintaining cardiovascular homeostasis.

### *Trimethylamine N-oxide (TMAO)*

Trimethylamine N-oxide (TMAO) is one of the most extensively investigated gut microbiota–derived metabolites in cardiovascular research. TMAO is generated through a two-step metabolic process in which dietary nutrients such as choline, phosphatidylcholine, and L-carnitine are metabolized by gut bacteria into trimethylamine (TMA), which is subsequently oxidized in the liver by flavin-containing monooxygenases to form TMAO. [1, 2, 12]

Elevated circulating TMAO levels have been associated with increased risk of cardiovascular events, including myocardial infarction, stroke, and atrial fibrillation. [1, 2, 11] Mechanistically, TMAO promotes systemic inflammation, oxidative stress, endothelial dysfunction, and myocardial fibrosis**,** processes that contribute to the formation of an arrhythmogenic substrate within the atria. [2, 6, 12]

Experimental studies suggest that TMAO may activate the NLRP3 inflammasome and the NF-κB signaling pathway, leading to increased production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). [4, 6, 10, 13, 14] In addition, TMAO has been shown to influence cardiac electrophysiology by promoting calcium-handling abnormalities, connexin remodeling, and atrial fibrosis, thereby increasing susceptibility to atrial arrhythmias. [5, 6, 10]

TMAO may also affect autonomic nervous system regulation. Experimental studies have demonstrated that TMAO can enhance sympathetic activity through stimulation of cardiac autonomic ganglia, potentially facilitating both supraventricular and ventricular arrhythmias. [6, 15]

### *Lipopolysaccharide (LPS)*

Lipopolysaccharide (LPS) is a major structural component of the outer membrane of Gram-negative bacteria and represents a potent pro-inflammatory endotoxin. In conditions of intestinal dysbiosis, increased intestinal permeability often referred to as "leaky gut" may allow LPS to translocate from the intestinal lumen into systemic circulation. [3, 4, 16]

Circulating LPS activates Toll-like receptor 4 (TLR4) on immune cells and cardiomyocytes, triggering downstream signaling pathways involving MyD88 and NF-κB activation. [3, 10, 17, 18, 19, 20] These pathways stimulate the release of pro-inflammatory cytokines and promote

activation of the NLRP3 inflammasome, a key molecular complex involved in atrial inflammation and fibrosis. [4, 10, 16, 21, 22]

In the context of atrial fibrillation, LPS-induced inflammation may contribute to both structural and electrical remodeling of the atria. Experimental studies suggest that inflammatory signaling can alter calcium channel expression, shorten atrial effective refractory periods, and disrupt gap junction organization through changes in connexin proteins, including connexin 40 and connexin 43. [1, 3, 6, 10] These electrophysiological alterations promote conduction heterogeneity and facilitate the formation of re-entry circuits that sustain atrial fibrillation.

### *Phenylacetylglutamine (PAGln)*

Phenylacetylglutamine (PAGln) is a gut microbiota–derived metabolite generated from the microbial metabolism of phenylalanine into phenylacetic acid, which is subsequently conjugated with glutamine in the host liver. [1, 23] Recent studies have identified PAGln as a metabolite with significant cardiovascular relevance.

PAGln has been shown to interact with adrenergic receptors, including α2A, α2B, and β2 receptors, thereby enhancing sympathetic signaling pathways involved in cardiovascular regulation. [24] Through this mechanism, PAGln may contribute to increased cardiac excitability and facilitate the initiation and maintenance of atrial fibrillation.

In addition to its electrophysiological effects, PAGln has been associated with platelet hyperreactivity and prothrombotic activity, linking gut microbial metabolism to thromboembolic complications in cardiovascular disease. [24, 25] Elevated circulating PAGln concentrations have been reported to predict major adverse cardiovascular events, including myocardial infarction and stroke. [24] These findings suggest that PAGln may represent an important metabolic mediator connecting gut microbiota with arrhythmia-related cardiovascular risk.

### *Bile acids*

Bile acids represent another important group of metabolites influenced by gut microbiota activity. Primary bile acids synthesized in the liver undergo microbial transformation in the intestine, leading to the formation of secondary bile acids, which can exert systemic metabolic and signaling effects. [3, 5]

Alterations in bile acid metabolism have been reported in patients with atrial fibrillation. Certain primary bile acids, such as chenodeoxycholic acid (CDCA), may promote oxidative stress and inflammatory signaling through activation of NADPH oxidase and generation of reactive oxygen species (ROS). [3, 18] ROS production may subsequently trigger ATP release and activation of the NLRP3 inflammasome, contributing to atrial fibrosis and structural remodeling.

Some bile acid conjugates, including taurocholic acid (TCA), may also influence cardiac electrophysiology by modulating ion channel activity and intracellular calcium dynamics, potentially shortening the atrial effective refractory period and increasing susceptibility to arrhythmias. [3, 6, 18]

In contrast, certain secondary bile acids, such as ursodeoxycholic acid (UDCA), appear to exert protective effects by stabilizing cardiomyocyte membrane potential and reducing oxidative stress. [3, 18, 22] These findings highlight the complex and sometimes opposing effects of bile acid metabolism within the gut–heart axis.

### *Short-chain fatty acids (SCFAs)*

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate**,** are produced through microbial fermentation of dietary fiber in the colon. These metabolites play an important role in maintaining intestinal barrier integrity, regulating immune responses, and modulating systemic metabolic processes (Fig. 2). [9, 10, 26]

SCFAs exert potent anti-inflammatory effects by activating G protein–coupled receptors such as GPR41 and GPR43 and by inhibiting histone deacetylases (HDAC), which promotes differentiation of regulatory T cells and suppresses pro-inflammatory cytokine production. [6, 20, 25, 26, 27] By strengthening intestinal barrier function, SCFAs may also reduce systemic exposure to endotoxins such as LPS.

In addition to their immunomodulatory effects, SCFAs may influence cardiac electrophysiology. Experimental studies suggest that SCFAs can stabilize cardiac conduction by preventing pathological remodeling of gap junction proteins and improving intracellular calcium handling. [10, 18, 25] These mechanisms may reduce atrial fibrosis and electrical instability, suggesting a potential protective role of SCFAs in atrial fibrillation (Fig. 2).

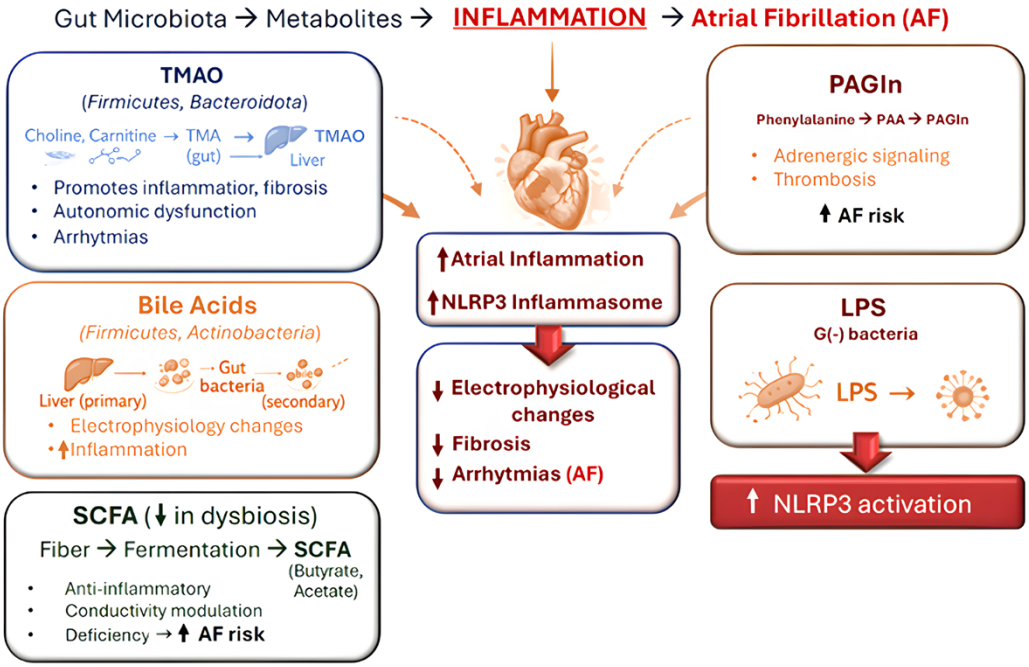


**Fig. 2.** Gut microbiota-derived metabolites and atrial fibrillation. This figure schematically presents the key gut microbiota-derived metabolites discussed in the manuscript (TMAO, secondary bile acids, SCFAs, PAGln, and LPS) and their proposed links to atrial fibrillation. The diagram illustrates the pathway from gut dysbiosis to systemic and atrial inflammation particularly via NLRP3 inflammasome activation leading to electrophysiological remodeling, fibrosis, and increased AF risk.

### *Summary of microbiota-derived metabolites*

Collectively, microbiota-derived metabolites represent a key mechanistic link between gut dysbiosis and atrial fibrillation. Pro-inflammatory metabolites such as TMAO, LPS, and PAGln appear to promote atrial inflammation, fibrosis, and electrical remodeling, whereas metabolites such as SCFAs and certain secondary bile acids may exert protective cardiovascular effects. These findings highlight the complex role of microbial metabolism in arrhythmogenesis and suggest that targeting microbial metabolic pathways may represent a promising therapeutic strategy for atrial fibrillation.

## Mechanisms linking gut dysbiosis and atrial fibrillation

The association between gut microbiota dysbiosis and atrial fibrillation (AF) is mediated by a complex network of metabolic, inflammatory, and neurohumoral mechanisms. Microbial imbalance may influence atrial electrophysiology and structural remodeling through the production of bioactive metabolites, activation of inflammatory pathways, modulation of autonomic nervous system activity, and disturbances in intracellular calcium handling. Together, these processes contribute to the development of an arrhythmogenic substrate that facilitates both the initiation and maintenance of atrial fibrillation. [1, 2, 3, 6]

### *Inflammation and immune activation*

Chronic systemic inflammation represents one of the central mechanisms linking gut dysbiosis with atrial fibrillation. Disruption of intestinal barrier integrity may lead to increased translocation of microbial components such as lipopolysaccharide (LPS) into the systemic circulation. LPS activates Toll-like receptor 4 (TLR4) expressed on immune cells and cardiomyocytes, triggering downstream signaling pathways involving MyD88 and nuclear factor κB (NF-κB) activation. [3, 10, 17, 18, 19, 20]

Activation of these inflammatory pathways stimulates the production of pro-inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These mediators contribute to systemic endotoxemia and promote inflammatory remodeling of atrial tissue. [1, 3, 10, 20, 25] A key molecular mediator in this process is the NLRP3 inflammasome, which has been increasingly recognized as an important driver of atrial inflammation and arrhythmogenesis. [2, 3, 10, 16, 21, 22]

Activation of the NLRP3 inflammasome leads to increased production of inflammatory cytokines and may promote cardiomyocyte injury, fibroblast activation, and extracellular matrix deposition, all of which contribute to structural remodeling of the atria and increased susceptibility to atrial fibrillation.

### *Atrial fibrosis and structural remodeling*

Structural remodeling of the atria, particularly the development of atrial fibrosis, is a key factor in the pathogenesis of atrial fibrillation. Several microbiota-derived metabolites, including TMAO and LPS, have been shown to promote pro-fibrotic signaling pathways.

Experimental studies suggest that TMAO can stimulate macrophage polarization toward a pro-inflammatory phenotype and activate molecular pathways such as MAPK and NF-κB, leading to increased cytokine production and inflammatory cell infiltration in atrial tissue. [4, 6, 10, 14] In addition, TMAO may trigger cardiomyocyte pyroptosis and release of damage-associated molecular patterns (DAMPs), which further stimulate fibroblast activation and differentiation into myofibroblasts. [10]

Activated myofibroblasts produce excessive extracellular matrix proteins through pathways including TGF-β1/Smad3 and Wnt/β-catenin signaling, resulting in progressive atrial fibrosis. [1, 25, 28, 29] Fibrotic remodeling disrupts the structural integrity of atrial tissue and creates regions of conduction heterogeneity that facilitate the formation of re-entry circuits sustaining atrial fibrillation.

### *Electrophysiological remodeling and calcium handling*

Gut microbiota dysbiosis may also contribute to atrial fibrillation through disturbances in cardiac tissue electrophysiology and intracellular calcium homeostasis. Inflammatory signaling and microbial metabolites have been shown to affect ion channel expression and gap junction organization in cardiomyocytes.

For example, LPS-induced inflammatory signaling may reduce the expression of L-type calcium channels, leading to decreased calcium current and shortening of the atrial effective refractory period (ERP). [1, 3, 6, 15] Shortened ERP facilitates the formation of re-entry circuits, which represent the fundamental electrophysiological mechanism sustaining atrial fibrillation.

Inflammatory mediators may also disrupt the function and distribution of gap junction proteins, including connexin 40 and connexin 43. Abnormal lateralization of connexins reduces conduction velocity and increases electrical heterogeneity within atrial tissue, further promoting arrhythmogenesis. [1, 10]

In addition, microbiota-derived metabolites such as TMAO and PAGln may influence intracellular calcium regulation by modulating CaMKII kinase activity and ryanodine receptor (RyR2) function, leading to abnormal calcium release from the sarcoplasmic reticulum and the generation of triggered electrical activity. [10]

### *Autonomic nervous system modulation*

The autonomic nervous system plays an important role in the initiation and maintenance of atrial fibrillation. Emerging evidence suggests that gut microbiota may influence autonomic regulation through both neural and metabolic pathways. [15, 18, 24]

Microbiota-derived metabolites such as TMAO and PAGln have been shown to interact with adrenergic signaling pathways, enhancing sympathetic nervous system activity and increasing cardiac excitability. [5, 15, 24] Experimental studies indicate that TMAO may stimulate autonomic ganglia, including the left stellate ganglion and ganglionated plexuses, thereby promoting sympathetic overactivation.

Increased sympathetic tone may shorten atrial refractoriness, enhance triggered activity, and facilitate the initiation of atrial fibrillation. Conversely, beneficial microbial metabolites such as short-chain fatty acids (SCFAs) may exert protective effects by reducing systemic inflammation and modulating autonomic balance. [18, 25]

### *Integrated pathophysiological model*

Taken together, gut microbiota dysbiosis contributes to atrial fibrillation through several interconnected mechanisms, including systemic inflammation, atrial tissue fibrosis, electrophysiological remodeling, and autonomic nervous system dysregulation. These processes interact to create a proarrhythmic substrate characterized by structural and electrical instability of atrial myocardium.

Understanding these mechanistic pathways provides important insight into the emerging concept of the gut–heart axis and suggests that modulation of gut microbiota and its metabolites may represent a promising strategy for the prevention and treatment of atrial fibrillation.

**Table 1.** Overview of gut microbiota-derived mechanisms in the pathogenesis of cardiac arrhythmias.

| Arrhythmia Type | Microbiota-Related Mechanisms | Key Metabolites/Pathways | Evidence/Notes |
|---|---|---|---|
| **Atrial Fibrillation (AF)** | Structural and electrical remodeling; atrial fibrosis; NLRP3 inflammasome activation | **TMAO, PAGln, LPS** (Pro-arrhythmic); **SCFAs** (Protective) | Strong correlation with gut dysbiosis; TMAO predicts AF recurrence after ablation [6, 10, 11, 30, 31] |
| **Ventricular Arrhythmias** | $Ca^{2+}$ handling instability; Cx43 lateralization; autonomic nervous system (ANS) modulation | **Propionate (SCFA)**, Phenylacetylglutamine (**PAGln**) | PAGln enhances adrenergic signaling; SCFAs stabilize electrical conduction via GPR41/43 [15, 18] |
| **Bradyarrhythmias** | Vagus nerve overstimulation; metabolic interference with pacemaker cells | **Bile Acids**, **TMAO** | Secondary bile acids can modulate sinoatrial node (SAN) function and heart rate. [3, 18] |

## Bidirectional relationship between atrial fibrillation and gut dysbiosis

Increasing evidence suggests that the relationship between gut microbiota dysbiosis and atrial fibrillation (AF) could be bidirectional. While alterations in gut microbial composition and microbial metabolite production may contribute to the development and progression of atrial fibrillation, the presence of AF and its associated cardiovascular conditions may in turn influence intestinal physiology and microbiota composition. [1, 3, 9]

On the one hand, gut dysbiosis may promote arrhythmogenesis through several interconnected mechanisms. Changes in microbial composition may increase the production of pro-inflammatory metabolites such as trimethylamine N-oxide (TMAO), lipopolysaccharide (LPS), and phenylacetylglutamine (PAGln), which have been implicated in systemic inflammation, oxidative stress, endothelial dysfunction, and myocardial structural remodeling. [1, 2, 3, 6, 32] These processes may contribute to atrial fibrosis, electrophysiological instability, and autonomic nervous system imbalance, thereby facilitating the initiation and maintenance of atrial fibrillation.

On the other hand, atrial fibrillation and its associated comorbidities that may themselves influence gut microbiota composition. Cardiovascular conditions frequently accompanying AF, including heart failure, hypertension, metabolic syndrome, and diabetes, are known to affect

intestinal perfusion, intestinal barrier function, and immune responses. [3, 9] Hemodynamic disturbances, reduced intestinal blood flow, and venous congestion may impair intestinal barrier integrity, promoting microbial translocation and dysbiosis.

In addition, several clinical factors common in patients with atrial fibrillation may further modify the gut microbiome. These include advanced age, polypharmacy, dietary patterns, and the use of medications such as antibiotics, proton pump inhibitors, and cardiovascular drugs. Such factors may alter microbial diversity and metabolic activity, potentially amplifying inflammatory and metabolic disturbances linked to cardiovascular disease.

Importantly, observational studies have suggested that the degree of gut microbiota dysbiosis may correlate with the severity and duration of atrial fibrillation. For example, patients with persistent or long-standing AF have been reported to exhibit more pronounced alterations in microbial composition and metabolic profiles compared with individuals with paroxysmal AF. [6, 9] This observation supports the hypothesis that chronic atrial remodeling and systemic inflammation may interact with microbial imbalance in a self-reinforcing pathological cycle.

Despite growing evidence supporting this bidirectional interaction, most currently available data are derived from observational human studies and experimental animal models. Therefore, while the association between gut dysbiosis and atrial fibrillation appears consistent, a definitive causal relationship has not yet been fully established. [8, 9] Further longitudinal studies and interventional trials are required to clarify whether modulation of the gut microbiota can influence the incidence, progression, or recurrence of atrial fibrillation.

## Therapeutic implications and microbiome-targeted strategies in atrial fibrillation

The growing understanding of the gut–heart axis has generated increasing interest in therapeutic strategies aimed at modulating gut microbiota composition and microbial metabolism. Although the role of microbiome-targeted interventions in atrial fibrillation (AF) remains an emerging field, several approaches have been proposed that may influence arrhythmia risk through anti-inflammatory, metabolic, and electrophysiological mechanisms. [3, 22, 33]

These strategies primarily include dietary interventions, probiotics and prebiotics, fecal microbiota transplantation (FMT), and pharmacological modulation of microbiota-derived metabolites**.**

### *Dietary interventions*

Diet is one of the most important determinants of gut microbiota composition and metabolic activity. Diets rich in dietary fiber, such as the Mediterranean diet, promote the growth of beneficial bacteria that produce short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate. [22, 33]

SCFAs exert multiple cardioprotective effects, including reduction of systemic inflammation, improvement of endothelial function, and stabilization of intestinal barrier integrity. These mechanisms may reduce atrial structural remodeling and inflammatory activation associated with AF. [3, 22, 33, 34] In addition, high-fiber diets have been associated with improvements in several AF risk factors, including hypertension, obesity, and metabolic dysfunction.

Some dietary compounds may also directly influence microbial metabolite production. For example, 3,3-dimethyl-1-butanol (DMB), a compound naturally present in extra virgin olive oil and

balsamic vinegar, has been shown to inhibit microbial trimethylamine (TMA) production, thereby reducing circulating levels of trimethylamine N-oxide (TMAO) in experimental models. [26, 28, 29]

### *Probiotics and prebiotics*

Probiotics and prebiotics represent another potential strategy for modulating gut microbiota composition. Probiotics, defined as live microorganisms that confer health benefits to the host, may improve intestinal barrier function and reduce systemic inflammation.

Supplementation with bacterial strains such as Lactobacillus and Bifidobacterium has been shown to strengthen intestinal barrier integrity and limit translocation of endotoxins such as lipopolysaccharide (LPS) into systemic circulation. [3, 15] By reducing systemic inflammatory burden, probiotics may indirectly influence cardiovascular risk factors associated with atrial fibrillation, including obesity, hypertension, and atherosclerosis. [1, 35]

Prebiotics, which are non-digestible dietary substrates that selectively promote the growth of beneficial bacteria, may increase the abundance of SCFA-producing microorganisms. Although clinical data specifically addressing AF remain limited, prebiotics have been shown to improve metabolic parameters and blood pressure regulation, suggesting a potential indirect benefit for arrhythmia prevention. [3, 34]

### *Fecal microbiota transplantation*

Fecal microbiota transplantation (FMT) represents a more direct method of restoring a healthy microbial ecosystem by transferring intestinal microbiota from a healthy donor to a recipient. Although primarily used for the treatment of recurrent *Clostridioides difficile* infection, FMT has recently gained attention as a therapeutic approach in cardiometabolic diseases. [3, 10, 18, 20, 36, 37, 38, 39]

Experimental studies have demonstrated that transplantation of microbiota from healthy donors to animal models with atrial fibrillation may reduce atrial fibrosis, decrease NLRP3 inflammasome activation, and improve cardiac electrophysiological stability. [3, 15, 33, 34, 36, 37, 38, 39] These findings suggest that restoration of microbial diversity may mitigate inflammatory and structural mechanisms involved in AF pathogenesis.

However, clinical evidence in humans remains limited, and further studies are required to determine the safety, feasibility, and therapeutic efficacy of FMT in cardiovascular disease.

### *Targeting microbiota-derived metabolites*

Another emerging therapeutic strategy involves targeting specific microbial metabolic pathways implicated in cardiovascular pathology. Among these, inhibition of trimethylamine (TMA) production represents one of the most actively investigated approaches.

As mentioned previously, compounds such as 3,3-dimethyl-1-butanol (DMB) can inhibit microbial enzymes responsible for TMA formation, thereby reducing circulating TMAO levels and attenuating inflammatory and fibrotic remodeling in experimental cardiovascular models. [28, 29, 40]

Additionally, omega-3 fatty acids have been suggested to influence gut microbiota composition and increase SCFA production while reducing pro-inflammatory microbial metabolites. These effects may contribute to improved endothelial function and reduced arrhythmia susceptibility. [41, 42]

Although these approaches remain largely experimental, targeting microbial metabolites may represent a promising strategy for precision medicine approaches in cardiovascular disease, particularly in conditions characterized by systemic inflammatory and metabolic dysregulation such as atrial fibrillation.

## Clinical perspectives

Despite promising experimental findings, microbiome-targeted therapies for atrial fibrillation remain in an early stage of development. Most available evidence derives from preclinical studies or observational clinical data. [3, 5, 18, 20, 21, 23, 36] Large randomized blinded clinical trials are therefore required to determine whether interventions targeting gut microbiota composition or microbial metabolism can effectively reduce AF incidence, progression, or recurrence.

Nevertheless, growing insights into the gut–heart axis suggest that modulation of intestinal microbiota may represent a novel complementary approach in the prevention and management of atrial fibrillation.

**Table 2.** Potential preventive strategies for atrial fibrillation, as the most extensively studied cardiac arrhythmia linked to the gut microbiota
SCFA — short-chain fatty acids; TMAO — trimethylamine N-oxide; FMT — faecal microbiota transplantation; AF — atrial fibrillation.

| Approach / Intervention | Mechanism / Goal | Evidence / Status | Sources |
|---|---|---|---|
| High-fiber / Mediterranean diet | ↑ SCFAs, ↓ TMAO, anti-inflammatory effect | Reduction of AF risk factors (hypertension, dyslipidemia, inflammation); animal and human observational data | [33, 43] |
| Prebiotics | ↑ SCFA-producing bacteria | Moderate effects on blood pressure and insulin; limited AF-specific data | [3, 34] |
| Probiotics | Microbiota modulation, ↓ inflammation | Effective in reducing risk factors; preclinical data for AF | [1] |
| FMT (Fecal Microbiota Transplantation) | Restoration of healthy microbiota | Animal models: AF reduction; human data are only beginning to emerge | [34, 36, 37] |
| **TMAO Inhibitors (DMB, IMC)** | ↓ TMAO, ↓ inflammation, ↓ fibrosis | Animal models: AF reduction; lack of large-scale clinical trials | [29, 40] |
| **SCFA Supplementation** | Anti-inflammatory and anti-fibrotic effects | AF reduction in animal models; limited human data | [33] |

## Limitations and future directions

Despite the growing knowledge linking gut microbiota dysbiosis with atrial fibrillation, several important limitations remain. First, the majority of currently available data originate from observational clinical studies and experimental animal models, which limits the ability to establish a clear causal relationship between gut microbiota alterations and atrial fibrillation development. [3, 6, 9]

Although associations between microbial composition, microbiota-derived metabolites, and AF have been consistently reported, the directionality and clinical significance of these interactions remain incompletely understood.

Another important limitation relates to the complexity and variability of the human gut microbiome. Microbiota composition is influenced by numerous factors, including age, diet, geographical location, medication use, and comorbidities such as obesity, diabetes, and cardiovascular disease. These confounding variables may significantly affect microbial profiles and complicate the interpretation of microbiome studies. [3, 6]

Furthermore, many studies investigating gut microbiota in AF involve relatively small sample sizes and heterogeneous patient populations, which may limit the generalizability of the findings. Differences in microbiome sequencing methods, bioinformatic analyses, and study designs may also contribute to variability across studies.

Future research should focus on large-scale longitudinal studies that can better define the temporal relationship between gut microbiota alterations and atrial fibrillation onset. In addition, randomized clinical trials are required to evaluate whether interventions targeting gut microbiota composition or microbial metabolic pathways can effectively prevent AF development or reduce arrhythmia recurrence after therapeutic interventions such as catheter ablation.

Advances in multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, may further improve our understanding of the complex interactions between the gut microbiome and cardiovascular physiology. Such integrative strategies may facilitate the identification of novel biomarkers and therapeutic targets within the gut–heart axis.

## Conclusions

Accumulating evidence indicates that gut microbiota dysbiosis plays an important role in the pathophysiology of atrial fibrillation through complex metabolic, inflammatory, and neurohumoral mechanisms. Microbiota-derived metabolites such as TMAO, LPS, and PAGln may promote atrial tissue inflammation, fibrosis, and electrophysiological remodeling, thereby contributing to the development of an arrhythmogenic substrate. In contrast, beneficial metabolites including SCFAs may exert protective effects by reducing systemic inflammation and stabilizing cardiac electrophysiology.

The concept of the gut–heart axis highlights the potential importance of intestinal microbiota as a novel factor influencing cardiovascular health and arrhythmia susceptibility. Although current findings strongly suggest a link between gut dysbiosis and atrial fibrillation, most available data are derived from observational studies and experimental models. Further large-scale longitudinal studies and blinded randomized clinical trials are required to clarify causal relationships and determine whether microbiome-targeted interventions may become effective strategies for the prevention and management of atrial fibrillation.

## Authors' contributions

Conceptualization, M.S.; Methodology, M.S., K.A.S.; Validation, K.B., J.S.; Investigation, M.S., K.A.S., K.B. and J.S.; Writing — original draft, M.S., K.A.S, Writing — review & editing, M.S., K.A.S., K.B. and J.S.; Visualization, M.S. and K.A.S.; Supervision, K.B. and J.S.

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## Data availability statement

The original contributions presented in this manuscript are included in the references section. Further inquiries can be directed to the corresponding author.

## Conflict of interest

The authors declare no conflict of interest.

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