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GUT MICROBIOTA IN CARDIOVASCULAR DISEASES. FROM MECHANISTIC INSIGHTS TO THERAPEUTIC PERSPECTIVES

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ABSTRACT

Cardiovascular diseases remain the leading cause of death worldwide, prompting continuous efforts to understand and treat their pathogenesis. In recent years, increasing attention has been paid to the role of the gut microbiome as a potential factor influencing the functioning of the cardiovascular system. The gut microbiota produces numerous bioactive metabolites, such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), which affect lipid metabolism, modulate systemic inflammation, and regulate blood pressure. SCFAs exhibit anti-inflammatory properties, whereas TMAO is associated with an increased risk of cardiovascular events.

Gut dysbiosis, defined as an imbalance in the intestinal microbiome, promotes chronic inflammation, increased intestinal barrier permeability, and activation of mechanisms that contribute to the development of atherosclerosis. This paper discusses the role of the gut microbiome in the pathogenesis of selected cardiovascular diseases, such as atherosclerosis, arterial hypertension, heart failure, and cardiac arrhythmias. Findings from observational and cohort studies reported in numerous scientific publications indicate characteristic alterations in the gut microbiota of patients with these conditions, although these relationships are primarily associative in nature.

The paper also presents potential strategies for modulating the gut microbiota through the use of a properly balanced diet, as well as probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT). Despite the growing body of evidence supporting a strong link between alterations in the gut microbiota and the development of cardiovascular diseases, there are still limitations in therapeutic approaches, including the lack of standardized research methods, high interindividual variability in microbiota composition, and a limited number of causal studies.

Future research directions should therefore include the development of personalized medicine, the application of multi-omics techniques, and the use of postbiotics. A better understanding of the interactions between the gut microbiota and the development and progression of cardiovascular diseases may contribute to the development of more effective treatment strategies.

KEYWORDS

Gut Microbiota, Cardiovascular Diseases, Short-Chain Fatty Acids (SCFAs), Trimethylamine N-oxide (TMAO), Atherosclerosis, Arterial Hypertension, Probiotics, Prebiotics, Synbiotics, Multi-Omics

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Introduction

Cardiovascular diseases (CVD) remain the leading cause of death in developed countries. The World Health Organization (WHO) reported that in 2022, nearly 20 million people worldwide died from cardiovascular diseases. Risk factors such as arterial hypertension, diabetes, hypercholesterolemia, nicotine dependence, and a sedentary lifestyle account for only a proportion of CVD cases; therefore, it is important to investigate new pathophysiological mechanisms underlying cardiovascular diseases. Studies conducted over the past decade aimed at modifying the development of CVD have revealed unexpected interactions between dietary intake, gut microbiota metabolism, and the host [1].

The surface area of the human gastrointestinal (GI) mucosa is approximately 200–300 m² and is colonized by 10^{13}–10^{14} bacteria representing around 400 different species and subspecies [2]. The entire gut microbiome functions as an endocrine organ, generating bioactive metabolites that can influence host physiology. The microbiota interacts with the host through a number of pathways, including the trimethylamine (TMA)/trimethylamine N-oxide (TMAO) pathway, the short-chain fatty acid pathway, and the primary and secondary bile acid pathways. These mechanisms directly contribute to an increased risk of metabolic-related diseases such as diabetes, hypertension, atherosclerosis, and chronic kidney disease [2].

The aim of this paper is to present the current state of knowledge on the relationship between the gut microbiota and cardiovascular diseases (CVD), to discuss key pathophysiological mechanisms, and to outline potential therapeutic applications.

Characteristics of the Gut Microbiome

The composition of the gut microbiome varies among individuals and depends on numerous factors, including diet, genetic diversity, environment, physical activity, age, and the use of medications, particularly antibiotics [3].

The intestinal microenvironment primarily supports the growth of bacteria belonging to seven dominant phyla: Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria. The gut microbiota performs several functions in the human body, including protective, structural, and metabolic roles. Its metabolic functions include the conversion of indigestible carbohydrates into short-chain fatty acids (SCFAs), degradation of xenobiotics, synthesis of vitamins (including B vitamins and vitamin K), transformation of bile acids, and the metabolism of choline into trimethylamine (TMA) and trimethylamine N-oxide (TMAO) [4].

Mechanisms Linking the Cardiovascular System and the Gut Microbiota

Bacterial metabolites play a crucial role in the modulation of the cardiovascular system. The main products of microbial fermentation of dietary fiber are short-chain and medium-chain fatty acids (SCFAs), with acetate, butyrate, and propionate being the most abundant metabolites. The majority of the literature linking the gut microbiota to human diseases suggests that SCFAs may act as potential factors in the prevention or mitigation of diseases such as obesity, diabetes, intestinal immune disorders, hypertension, kidney disease, cancer, and both alcoholic and non-alcoholic fatty liver disease (NAFLD) [1].

Butyrate serves as the primary energy source for colonic epithelial cells [5], exhibits anti-inflammatory effects through inhibition of the transcription factor NF-κB [6], and improves the integrity of the intestinal barrier [7]. Propionate has lipid-lowering properties [8] and regulates the process of gluconeogenesis [9]. Acetate, in turn, influences lipid metabolism [5] and regulates blood pressure [10].

An important factor affecting the cardiovascular system is the previously mentioned trimethylamine N-oxide (TMAO). TMAO is formed in the liver through the oxidation of trimethylamine (TMA) by flavin-containing monooxygenase (FMO3) [11]. Trimethylamine is produced by gut bacteria from dietary precursors such as choline, trimethylglycine, and L-carnitine [12]. Elevated levels of TMAO are associated with an increased risk of cardiovascular events [13], mainly by enhancing platelet aggregation [14], activating macrophages, and promoting the formation of so-called foam cells [12].

One of the major causes of cardiovascular diseases is chronic inflammation resulting from disturbances in the gut microbiota [15], which plays a key role in regulating immune homeostasis and inflammatory responses [1]. Lipopolysaccharides (LPS), which are components of the cell wall of Gram-negative bacteria residing in the gut, may enter the systemic circulation in cases of increased intestinal permeability [7] and can, among other effects, activate TLR4 receptors [1], induce the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 [16], as well as increase endothelial dysfunction [17] and accelerate the development of atherogenesis [18].

The Role of the Gut Microbiome in Specific Cardiovascular Diseases (CVD)

Atherosclerosis

Atherosclerosis is a chronic inflammatory process of the arterial walls, in which gut dysbiosis may play a significant role [18]. Patients with atherosclerosis often exhibit characteristic changes in gut microbiome composition, including a reduced number of SCFA-producing bacteria [19], decreased gut microbiota diversity [18], and an increased abundance of pro-inflammatory bacteria such as Enterobacteriaceae [20]. Gut dysbiosis also contributes to the induction of atherogenic mechanisms, including increased platelet aggregation [14], endothelial dysfunction [21], elevated TMAO production [12], and disturbances in lipid metabolism [8].

In a prospective cohort study by Ljung Wang et al., 2021, the relationship between the gut microbiota and therapeutic response in patients with coronary artery disease treated with statins was examined. A total of 836 patients were divided into two study groups. The first group included patients who responded well to statin therapy, showing a reduction in LDL cholesterol levels. The second group comprised patients with a poor response to statin therapy. Gut microbiota sequencing was performed on stool samples from both groups. In the first group, an increase in bacteria from the Lactobacillus and Akkermansia families was observed, which had beneficial effects on the course of atherosclerosis in these patients. In contrast, the second group showed an increase in bacteria from the Faecalibacterium and Holdemanella genera, which potentially contributed to a reduced statin response and impaired lipid metabolism. This study demonstrated that the gut microbiota - depending on its composition - may serve as a determinant in the development and progression of atherosclerosis in patients with coronary artery disease. Gut bacteria can positively influence cholesterol metabolism, reduce arterial inflammation, and modify statin metabolism, which exerts direct anti-atherosclerotic effects [22].

In one of the largest cohort studies, conducted by Budoff MJ et al., 2025, 6,767 participants were recruited. The study aimed to investigate the potential association between the gut microbiota-dependent metabolite TMAO and the development of atherosclerosis-related cardiovascular events in the general population. Participants who were asymptomatic at baseline were divided into five quintiles based on TMAO levels, with the lowest quintile serving as the control group and the higher quintiles representing groups with progressively increasing TMAO concentrations. TMAO levels were measured at baseline and after five years, allowing for assessment of temporal increases in this metabolite and thereby improving the study's reliability. A total of 852 atherosclerosis-related cardiovascular events, such as myocardial infarction and stroke, were recorded. Compared to the control group, the hazard ratio (HR) increased progressively across the quintiles, reaching 1.33 in the highest quintile, indicating that patients with the highest TMAO levels had a 33% higher risk of cardiovascular events than those in the first group. This study provided strong evidence for a microbiota-dependent association between elevated TMAO levels and increased cardiovascular risk [23].

Arterial Hypertension

Arterial hypertension affects approximately 1.13 billion people worldwide and is a leading cause of cardiovascular events [16]. Increasing evidence indicates a strong association between the gut microbiome and blood pressure regulation [10].

In a study by Jing LV et al., 2023, the relationship between gut microbiota composition and blood pressure was assessed in adults with hypertension. The study recruited 87 individuals with arterial hypertension as the study group and 45 healthy individuals as the control group. Participants' ages ranged from 18 to 80 years. Stool samples were collected from all participants and subjected to 16S rRNA sequencing. In addition, standard measurements of systolic and diastolic blood pressure, anthropometric assessments, and metabolic evaluations were performed. The results revealed significant differences in gut microbiota composition between the control and study groups. Moreover, hypertensive women exhibited an increase in unspecified bacteria, whereas healthy women showed higher levels of bacteria from the Leuconostocaceae family and Weissella. In men, no such differences were observed. These findings indicate a relationship between gut microbiota characteristics and arterial hypertension in humans and suggest that gut dysbiosis may play a significant role in the pathogenesis of hypertension [24].

A classical observational study by Q Yan et al., 2017, compared the gut microbiota composition of patients with hypertension to that of healthy individuals. The study included 120 participants divided into two groups. The control group consisted of 60 healthy individuals matched to the study group for sex, body mass, and age, while the study group included 60 patients with primary arterial hypertension. Stool samples from both groups were subjected to metagenomic whole-genome sequencing (shotgun sequencing) of the gut microbiome. The microbiota were analyzed for species-level diversity in both groups. The study group exhibited a higher abundance of opportunistic bacteria, including Klebsiella spp., Streptococcus spp., and Parabacteroides merdae, as well as a reduced abundance of SCFA-producing bacteria such as Roseburia spp. and Faecalibacterium prausnitzii. The study also found that the gut microbiota of hypertensive individuals displayed a higher metabolic potential related to LPS biosynthesis, which may promote increased inflammation, impaired intestinal barrier function, and ultimately contribute to the development of hypertension. These results suggest that gut dysbiosis is characteristic of individuals with arterial hypertension. Changes in the gut microbiota of hypertensive patients include a reduction in health-associated bacteria and an increase in bacteria that stimulate inflammatory processes [25].

Table 1. Comparison of studies investigating the correlation between arterial hypertension and gut microbiota diversity

Aspect	Jing Lv 2023	Q Yan 2017
Study type	Clinical, cross-sectional	Clinical, observational
Number of participants	Study group: 87; Control group: 45	Study group: 60; Control group: 60
Methods	16S rRNA + metagenomics	Shotgun metagenomics
Main finding	Microbiota differences associated with BP; sex-specific differences	Reduced diversity and dysbiosis in hypertensive individuals
Mechanisms	Functional microbiota profiles correlated with SBP	Fewer SCFA-producing bacteria, more pathogens

Heart Failure

In addition to the well-documented associations between the gut microbiota and the development and progression of atherosclerotic changes that may lead to cardiovascular events, the impact of the gut microbiome on the course of heart failure has also been investigated.

In a randomized clinical trial by Awoyemi A. et al., 2021, 132 patients with heart failure and reduced left ventricular ejection fraction (LVEF < 40%) were recruited. The study aimed to assess whether modification of the gut microbiota using a probiotic or an antibiotic could improve cardiac function in these patients. All participants had HFrEF < 40% and were classified as NYHA class II or III despite receiving optimal treatment for at least three months.

Forty-eight patients received rifaximin at a dose of 550 mg twice daily. Fifty-one patients were administered a probiotic twice daily (250 mg per dose) containing the yeast strain *Saccharomyces boulardii*. The control group, comprising 52 patients, received standard heart failure therapy. After three months, heart failure parameters were reassessed in all groups. In the rifaximin group, mean heart function declined by 1.2%, whereas in the probiotic group, it declined by 0.2%. No significant effects were observed on LVEF, gut microbiota composition, inflammatory markers, or TMAO levels. Routine administration of rifaximin or *S. boulardii* strains did not result in a significant improvement in left ventricular function among the participants.

These findings suggest that broad probiotic or antibiotic interventions may be insufficient to meaningfully influence the gut microbiota [26].

Cardiac Arrhythmias

Increasing evidence indicates a relationship between the gut microbiome and cardiac arrhythmias, particularly atrial fibrillation (AF) [27].

In a prospective cohort study by Palmu J. et al., 2023, the association between gut microbiota composition and the presence and risk of developing AF was investigated. A total of 6,763 participants from the FINRISK 2002 study were recruited. The median follow-up period for the occurrence of AF from the time of microbiota sample collection was 15 years. Stool samples collected at baseline were analyzed using 16S rRNA sequencing. Clinical data regarding AF were obtained from medical registries and participants' medical histories. Participants were divided into three groups: the control group included individuals without AF at baseline. The remaining two study groups included participants with AF prior to the study (116 participants) and participants who developed AF during the cohort follow-up (539 participants). Analysis of the gut microbiota in both study groups revealed an increased abundance of *Enorma* and *Bifidobacterium species*, whereas these bacteria were not elevated in the control group. Overall bacterial diversity, however, remained largely unchanged across all groups. Changes in gut microbiota composition may be associated with both existing and future development of AF. This study suggests that the gut microbiome may act as a risk factor or a marker for AF [28].

In a clinical study by Wang Y. et al., 2023, differences in gut microbiota composition were examined in patients undergoing coronary artery bypass grafting (CABG) who developed postoperative atrial fibrillation (POAF) compared to those who did not experience this complication. Stool samples were collected preoperatively, and 16S rRNA sequencing was used to analyze the gut microbiota. The study group, consisting of patients who developed POAF, included 45 participants, while the control group included 90 participants. Distinct differences in gut microbiota composition were observed. In the study group, there was an increased abundance of bacteria from the genera *Lachnospira*, *Acinetobacter*, *Veillonella*, and *Aeromonas*. Conversely, these patients exhibited a decreased abundance of *Escherichia*, *Shigella*, *Klebsiella*, *Streptococcus*, *Brevundimonas*, and *Citrobacter*. The observed differences in gut microbiota composition correlated with the subsequent development of POAF. This study suggests that gut microbiota composition may influence susceptibility to arrhythmias following surgical procedures [29].

Table 2. Comparison of clinical studies analyzing the relationship between gut microbiota and cardiac arrhythmias

Feature	Palmu et al., 2023	Wang et al., 2023
Study type	Prospective cohort study (population-based)	Observational study
Population	General adult population (from FINRISK 2002)	Patients undergoing CABG (coronary artery bypass grafting)
Number of participants	6,763	135 (45 POAF + 90 control)
Study groups	- AF present (n = 116) - Incident AF (n = 539) - No AF (control group)	- POAF (n = 45) - No POAF (n = 90)
Type of arrhythmia	Atrial fibrillation (AF) – both preexisting and new-onset cases	Postoperative atrial fibrillation (POAF)
Follow-up period	Median ~15 years	Short-term postoperative follow-up
Timing of sample collection	Baseline	Preoperatively
Microbiota analysis methods	16S rRNA sequencing	16S rRNA sequencing
Main microbiota findings	- Specific bacteria (e.g., *Enorma*, *Bifidobacterium*) associated with AF	- ↑ *Lachnospira*, *Acinetobacter*, *Veillonella* - ↓ *Escherichia-Shigella*, *Klebsiella*, *Streptococcus*
Nature of association	Associative (AF risk prediction)	Associative (predisposition to POAF)
Conclusions	Gut microbiota may serve as a biomarker for AF risk	Preoperative microbiota composition may influence POAF risk
Limitations	No intervention, no evidence of causality	Small sample size, lack of randomization, potential confounding factors
Clinical significance	Identification of potential microbiota biomarkers for AF	Potential application of microbiota in postoperative risk stratification

Modulation of the Gut Microbiome as a Therapeutic Strategy

In recent years, increasing attention has been paid to the modulation of the gut microbiome as a potential therapeutic strategy for the prevention and treatment of cardiovascular diseases (CVD). The close relationship between dysbiosis of the gastrointestinal tract - particularly the intestines - and the pathogenesis of atherosclerosis, hypertension, and cardiac arrhythmias has already been mentioned and involves inflammatory mechanisms, lipid metabolism, and the production of gut-derived metabolites such as TMAO [1].

One of the fundamental therapeutic strategies is the use of probiotics, which are live microorganisms that exert beneficial effects on the host [30]. The mechanisms of probiotic action include, among others, the production of short-chain fatty acids (SCFAs) [5], competition with pathogens for ecological niches [30], improvement of intestinal barrier integrity [6], and the synthesis of bioactive compounds [21]. The best-known bacterial strains with confirmed efficacy in the treatment and prevention of cardiovascular diseases include:

- *Lactobacillus plantarum*, which has hypocholesterolemic effects [8], reduces inflammation, and improves endothelial function [21];
- *Bifidobacterium bifidum*, which affects lipid metabolism [31], exhibits hypotensive effects [6], and modulates the microbiome [9];
- *Lactobacillus acidophilus*, which reduces LDL cholesterol [8], has anti-inflammatory effects [31], and improves insulin sensitivity [9].

In a meta-analysis conducted by Mo Zhang et al. in 2021, the effects of probiotic supplementation on lipid profile and blood pressure were examined. Patients were divided into two groups: the intervention group included 297 participants supplemented with probiotics contained in natural yogurts and fermented products, while the control group consisted of approximately 290 participants receiving a placebo or similar products without probiotics. After approximately 12 weeks of intervention, blood pressure parameters and lipid profiles were compared between the two groups. The intervention group showed significant reductions in total cholesterol, triglycerides, LDL cholesterol, and both systolic and diastolic blood pressure compared to the control group. Additionally, HDL cholesterol levels increased in the intervention group relative to controls. Although the effects were statistically significant for many parameters, not all exhibited a large effect size. The study demonstrated that probiotics can influence the gut microbiome, lower blood pressure, and positively impact lipid profiles [8].

Another factor that may significantly influence gut microbiome modulation is the use of prebiotics - non-digestible dietary components that promote the growth of beneficial gut bacteria [32]. The main prebiotics that contribute substantially to gut microbiome improvement include:

- Inulin, which increases SCFA production [5] and improves glucose metabolism [9];
- Oligofructose, which stimulates the growth of *Bifidobacterium spp.* [32] and exhibits hypolipidemic effects [8];
- Galactooligosaccharides, which have anti-inflammatory effects [31].

Another therapeutic tool in the prevention of cardiovascular diseases may be synbiotics, which are combinations of probiotics and prebiotics that act synergistically [32]. Synbiotics appear to be more effective than individual probiotics or prebiotics. The main advantages of synbiotics include better probiotic survival, greater product stability [30], and more effective intestinal colonization [31].

Increasing interest is also being directed toward fecal microbiota transplantation (FMT), which involves transferring the microbiome of a healthy donor to the gastrointestinal tract of a recipient. Although currently primarily used to treat *Clostridioides difficile* infections, FMT may in the future be applied to the treatment of CVD. Further research is needed, particularly to assess its safety and efficacy [33]. Potential applications of this method include: modification of the gut microbiome in atherosclerosis [18], treatment of resistant hypertension [34], and prevention of cardiovascular complications [27]. The main limitations and risks associated with FMT include the potential transmission of pathogens from donor to recipient, unpredictable long-term effects, lack of standardized procedures, and ethical concerns [27].

The most important element of gut microbiome modulation to date is diet. A diet rich in fiber, polyphenols, and unsaturated fatty acids, such as the Mediterranean diet, promotes increased gut microbiome diversity while reducing TMAO levels. Conversely, a diet high in red meat and saturated fats may promote CVD risk [35].

Challenges, Limitations, and Future Directions of Research

Despite the growing evidence indicating the significant role of the gut microbiome in the pathogenesis and prevention of cardiovascular diseases (CVD), these findings still face numerous challenges. One of the main limitations is the high variability in gut microbiome composition between individuals, resulting from factors such as age, sex, diet, lifestyle, genetics, and medication use [36]. This variability complicates the development of therapeutic interventions and the identification of universal biomarkers [37].

Another limitation is the lack of clear causal evidence. Unfortunately, most available studies are observational, making it difficult to distinguish whether changes in gut microbiome composition are a cause or a consequence of CVD [38].

A further limitation concerns the standardization of research methods. Differences in bacterial DNA sequencing techniques and data interpretation create challenges in comparing results across studies [39]. Methodological issues also involve DNA extraction protocols, the selection of sequencing regions, and sample storage standards [40].

Finally, safety considerations are also critical. Interventions such as fecal microbiota transplantation (FMT) carry the risk of pathogen transfer from donor to recipient [35].

In the context of future research, personalized medicine approaches based on an individual's gut microbiome profile, real-time monitoring, and tailored dietary recommendations may become increasingly important [32]. Identification of disease-specific microbiome profiles, predictive biomarkers for treatment response, and machine learning algorithms could enhance the effectiveness of therapeutic interventions while reducing the risk of adverse effects [18, 21, 27, 37].

A promising direction may be the use of so-called postbiotics, metabolites produced by gut bacteria, such as short-chain fatty acids (SCFAs). Their direct application could achieve therapeutic effects without the need to modify the entire gut microbiome [41].

Ongoing technological advancements, including multi-omics approaches - metagenomics and metabolomics - enable a comprehensive strategy for gut microbiome research. Integrating these data with clinical findings and patient symptoms may contribute to a better understanding of the mechanisms underlying cardiovascular diseases [42].

Conclusions

The gut microbiota plays a significant role in the pathogenesis of cardiovascular diseases (CVD), influencing metabolic, immunological, and inflammatory processes within the host organism. Key bacterial metabolites, such as short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), can exert either protective or pro-atherogenic effects, thereby impacting the development of hypertension, myocardial ischemia, and cardiac arrhythmias. Gut dysbiosis, characterized by reduced bacterial diversity, an increase in pro-inflammatory bacteria, and endothelial dysfunction-including increased intestinal barrier permeability-is associated with enhanced inflammatory processes and the progression of CVD.

There is evidence linking gut microbiota composition with the development of specific cardiovascular conditions, including atherosclerosis, hypertension, and arrhythmias. The gut microbiota may also influence the efficacy of statin therapy, suggesting its potential role in personalized medicine. Modulation of the gut microbiome through diet, probiotics, prebiotics, and newer approaches such as fecal microbiota transplantation (FMT) or the use of synbiotics represents a promising strategy for the treatment and prevention of CVD. However, current clinical studies still require further verification and development.

The main limitations of existing research include inter-individual variability in gut microbiota, insufficient numbers of interventional studies, and a lack of standardization in research methodologies. Future research directions should focus on the integration of large-scale multi-omics data, including metabolomics and metagenomics, as well as the development of personalized therapeutic strategies based on individual gut microbiome profiles. A better understanding of the gut-heart axis may contribute to the development of novel preventive and therapeutic approaches for cardiovascular diseases, which is increasingly important given their rising global prevalence.

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