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REVIEW ARTICLE

# Gut Microbiota and Vascular Diseases: An Update

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**Abstract**

Vascular diseases, including atherosclerosis, aneurysms, and vascular calcification, are a leading cause of morbidity and mortality worldwide. In past decades, the gut microbiota has been found to be an indispensable population exerting effects on hosts under physiological and pathological conditions. Gut microbiota-derived metabolites, such as trimethylamine-N-oxide and short-chain fatty acids, mediate these effects by regulating vascular cells systematically. Translation of research knowledge to clinical scenarios has led to the development of new therapies including dietary interventions and metabolite inhibitors. This review describes recent advancements in understanding of the interplay between the gut microbiota and vascular dysfunction, and potential treatments for vascular diseases.

**Keywords:** Gut microbiota; atherosclerosis; aneurysms; vascular calcification; therapy

## Introduction

Vascular systems, consisting primarily of the tunica intima, tunica media, and adventitia, circulate blood through the entire body, and provide oxygen and nutrients for diverse tissues. Blood vessels are not simply elastic tubes but are a dynamic microenvironment responding to stimuli. Vascular homeostasis is maintained by cell types including endothelial cells, vascular smooth muscle cells (VSMCs), fibroblasts, macrophages, and adipocytes. Disruption of vascular homeostasis by various risk factors, such as diabetes, hyperlipidemia, smoking, high blood pressure, and obesity, lead to vascular remodeling, in a structural and functional adaptive process. Consequently, various vascular diseases, such as atherosclerosis, vascular calcification (VC), and aneurysms, can arise and threaten human health.

In the human gastrointestinal tract, more than 100 trillion microorganisms, termed the gut microbiota, symbiotically evolved together with the host [1, 2]. Substantial evidence has demonstrated that the gut microbiota acts as an "invisible organ" affecting human physiology, metabolism, and immunity homeostasis [1–3]. A well-balanced gut microbiota preserves host health, and gut microbiota dysbiosis facilitates inflammatory and metabolic diseases, such as vascular diseases [1, 4]. A deeper understanding of the mechanisms of gut microbiota-host interaction has enabled novel therapeutic options for delaying or even reversing vascular diseases. In this narrative review, we summarize recent progress in

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the advancing field of the gut microbiota and vascular remodeling processes. We searched manuscripts by using the keywords ("gut microbiota" or "microorganism" or "TMAO") and ("atherosclerosis" or "vascular calcification" or "aneurysms") in PubMed, and focused on studies published in the past 3 years.

## Atherosclerosis

Atherosclerosis, one of the most common vascular diseases, is characterized by endothelial dysfunction, lipid accumulation, infiltration of inflammatory cells, and the formation of plaques, thus ultimately leading to vascular stenosis and ischemic events including myocardial infarction, cerebral infarction, mesenteric artery ischemia, and peripheral artery disease (PAD) [5]. Low and oscillatory shear stress activates endothelial inflammation and contributes to the pathogenesis of atherosclerosis and restenosis [6, 7]. Although gut microbiota dysbiosis has been observed in several studies, the conclusions have been ambiguous, largely because of differences in study populations, criteria, and methods [8, 9]. Recently, Choroszy's analysis of 21 studies has highlighted that *Enterobacteriaceae*, *Lactobacillus*, and *Streptococcus* are elevated, while *Bacteroidetes* and *Lachnospiraceae* are diminished, in patients with coronary artery disease (CAD) [10]. These changes might correlate with the progression of atherosclerosis. Gut microbiota alterations in patients with PAD remain unclear, including whether these patients show similar trends in microbiota changes to patients with CAD. The precise roles of specific taxa in atherosclerosis also remain uncertain. For instance, *Lactobacillus* has traditionally been considered to have anti-atherosclerotic roles by lowering lipids but is paradoxically elevated in patients with CAD [11, 12]. Whether quantitative changes in *Lactobacillus* protects against CAD development remains to be determined.

A plethora of evidence, including shifts in gut microbiota-modified metabolites in patients with CAD, has suggested that metabolites directly link microbiota dysbiosis to vascular atherosclerosis.

Trimethylamine-N-oxide (TMAO), a metabolite produced from dietary precursors in the liver by trimethylamine (TMA) oxidization, has been explored in previous studies [13, 14]. Extensive clinical and animal studies have concluded that TMAO promotes atherosclerosis through multiple mechanisms, such as cholesterol accumulation, inflammatory cell recruitment, and endothelial dysfunction [3, 13–15]. Elevated TMAO levels predict greater incidence of adverse events in patients with CAD and PAD [16]. Promisingly, TMAO precursors and TMAO are targets for vascular protection. In contrast to TMAO, short-chain fatty acids (SCFAs), generated from fermented fibers, exert beneficial effects on vascular inflammation and lipid disruption [17, 18]. Recently, Haghikia's research has emphasized that propionic acid (PA), an important SCFA, significantly decreases atherosclerotic lesions in HFD-induced *Apoe*$^{-/-}$ mice [19]. This protective effect is mediated by inhibition of cholesterol transporters and lowering of cholesterol levels (Figure 1) [19]. Interestingly, oral administration of 500 mg of PA twice daily for 8 weeks markedly decreases cholesterol levels in patients with hypercholesterolemia, thus suggesting translational potential of this treatment in the future [19]. A larger long-term study is warranted to comprehensively evaluate the effects of PA on vascular walls and other tissues.

Considerable investigations have indicated the involvement of microbiota-derived tryptophan metabolites in vascular inflammation and atherosclerosis [20, 21]. Xue's updated work has established that, in addition to indolamine-2, 3-dioxygenase-1 (IDO1), indole-3-propionic acid (IPA), another tryptophan metabolite, is correlated with atherosclerosis, on the basis of microbiome-metabolome sequencing in patients [22]. IPA is diminished in atherosclerotic patients and *ApoE*$^{-/-}$ mice, whereas administration of IPA hinders atherosclerosis development in *ApoE*$^{-/-}$ mice [22]. The beneficial effects are due to increased cholesterol efflux in macrophages through modulation of the miR-142-5p/ABCA1 signaling pathway [22]. Phenylacetylglutamine plays a crucial role in atherosclerosis and in-stent stenosis, but the exact mechanisms remain unsubstantiated [23, 24]. Further studies on phenylacetylglutamine are anticipated.

Natural products are a group of bioactive components with robust ability to protect against vascular inflammation [25]. A body of updated studies have affirmed that these protective effects result from modulation of the gut microbiota, because the oral bioavailability of these natural products is low. Although previous investigations have

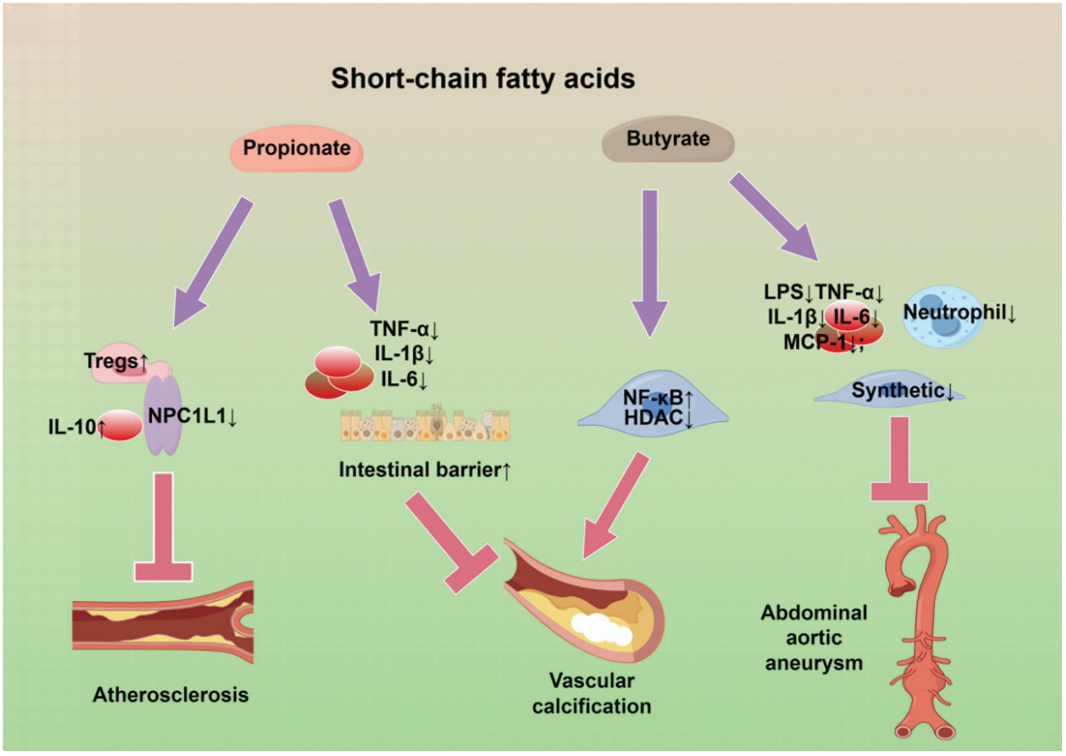


**Figure 1** Effects and Mechanisms of SCFAs in Vascular Diseases. Illustration made with Figdraw.

suggested that berberine minimizes plaque development, Ma's work has further verified that this observation is strongly associated with decreased TMAO generation through a vitamin-like effect downregulating the choline-TMA-TMAO pathway [26]. Importantly, oral administration of berberine for 4 months down-regulates plaque scores and TMAO levels in patients with atherosclerosis compared with those receiving a statin plus antiplatelet drugs [26]. However, this evaluation was conducted through ultrasonography, which is less accurate than CT scans. Bicyclol, another herbal extract, has shown strong anti-atherosclerotic effects in high fat diet-induced murine models [27]. A metagenome-wide association study has revealed that bicyclol maintains the gut microbiota, and further preserves gut integrity and immunity [27]. Ginsenoside Rc, like other family members, alleviates atherosclerosis development by restoring the gut microbiota, particularly *Muribaculaceae*, *Lactobacillus*, *Ileibacterium*, *Bifidobacterium*, *Faecalibaculum*, *Oscillibacter*, *Blautia*, and *Eubacterium_coprostanoligenes*_group [28]. Consequently, the gut microbiota is an important mediator of the effects of natural products *in vivo*, and natural products may therefore find clinical applications. The results for berberine have been particularly encouraging, because berberine is an over-the-counter drug with demonstrated safety in time course studies. The long-term effects of berberine on atherosclerosis and the gut microbiota will be a topic of interest for further studies.

## Vascular Calcification

Unlike atherosclerosis, VC is characterized by the deposition of calcium phosphate in the vascular intima and media [29, 30]. Progression of VC is a strictly regulated biological process associated with aging, diabetes, and chronic kidney disease (CKD) [30]. An elevated incidence of VC is observed in patients with CKD, largely because of excessive uremic toxins, and dysmetabolism of calcium and phosphate. Gut microbiota dysbiosis and abnormal metabolites also contribute to VC [31–33]. In a pilot study including 44 patients with CKD with peritoneal dialysis, with or without VC, Merino-Ribas's research has identified alterations in *Coprobacter*, *Coprococcus 3*, *Lactobacillus*,

and *Eubacterium eligens* group in the gut, and *Cutibacterium*, *Pajaroellobacter*, *Devosia*, *Hyphomicrobium*, and *Pelomonas* in the blood [34]. Moreover, *Eubacterium eligens* in the gut and *Devosia genus* in the blood correlate with mortality in patients with CKD and therefore may predict prognosis in these patients [34]. Additionally, Bao and colleagues have analyzed the gut microbiota of patients with high versus low calcification scores, undergoing hemodialysis [35]. In accordance with findings from a previous study, *Firmicutes*, *Actinobacteriota*, *Proteobacteria*, and *Bacteroidota* were found to be major bacteria in patients with CKD [35]. Unexpectedly, the researchers identified another two phyla: *Escherichia-Shigella* and *Ruminococcus*, which were positively and negatively associated with vascular calcification, respectively [35]. Discrepancies in findings across studies may be due to differences in dialysis styles, patient race, diet, and methods. To date, conclusions have been largely based on the population with CKD. Investigating the gut microbiota in patients with age-associated calcification in clinical settings will be a necessary next step to advance research [36].

An altered gut microbiota in patients with CKD with VC detrimentally affects vascular homeostasis and further contributes to VC progression [31, 32]. Various uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, originate from the gut microbiota [37]. These factors facilitate VC development through inflammatory activation and VSMC osteogenic changes [38, 39]. Although dietary interventions greatly decrease levels of indoxyl sulfate and p-cresyl sulfate, direct evidence of the effects of dietary intervention on VC remains insufficient [40]. TMAO is elevated in patients with CKD with VC, and has been verified as an independent risk factor for VC in patients undergoing hemodialysis [41, 42]. Furthermore, excessive supplementation with TMAO in rats with CKD promotes aortic calcification, whereas this effect is reversed by antibiotic treatment [42]. *In vitro* and *ex vivo* studies have demonstrated that TMAO enhances calcium/phosphate induced osteogenic differentiation of VSMCs, in a process mediated by NLRP3 and NF-κB stimulation [42]. Intriguingly, the influence of SCFAs on VC varies (Figure 1). In a cohort of 92 patients, the level of propionate has been negatively associated with vascular calcification [43]. To validate the role of propionate in VC, one study has supplemented vitamin D3 and nicotine induced rats with propionate, orally and rectally [43]. In this model, propionate significantly decreases VC progression and is accompanied by *Akkermansia* enrichment [43]. Furthermore, addition of *Akkermansia* hinders the development of VC; consequently, *Akkermansia* may mediate the protective effects of propionate [43]. Although butyrate has been speculated to be a protective factor against VC, Zhong's work has indicated that butyrate accelerates VC in vitamin D3 induced mice [44]. In VSMCs with high phosphate, butyrate promotes calcification and activates osteogenic genes [44]. Mechanistic analysis has revealed that this phenomenon is correlated with HDAC inhibition and NF-κB signaling [44]. Nevertheless, observations have confirmed that propionate does not change mRNA expressions of osteogenic genes in high phosphate induced VSMCs, in contrast to Yan's data [43, 44]. The use of different inducers of VC, namely, vitamin D3 and nicotine, or high phosphate, may account for the inconsistent results across studies. Another VC animal model induced by a high fat diet was not studied previously [45]. Given the diverse types of gut microbiota-derived metabolites, the precise roles of metabolites must be explored in the future [37] to provide further evidence regarding therapeutic targets of VC, given that no effective pharmacological strategies for VC have been developed in clinical settings.

## Abdominal Aortic Aneurysm and Intracranial Aneurysm

Abdominal aortic aneurysm (AAA) is defined as segmental enlargement of the abdominal aorta above 50% of its normal diameter [46]. Rupture of AAA always causes death, although no effective pharmacological therapy is available to delay AAA development [47]. Emerging evidence suggests that the gut microbiota is robustly involved in AAA progression [48]. In an analysis of 30 AAA patients, diminished *Bacteroidetes* has been observed [49]. Importantly, bacteria such as *Streptococcus* have been identified in blood samples and aneurysmal tissues, thus suggesting that bacterial translocation may contribute to human AAA development [49]. Although *Streptococcus* is associated with

mycotic AAA, the precise mechanisms underlying the role of *Streptococcus* in chronic AAA progression remain unclear [50, 51]. Recently, Tian's work has further profiled gut dysbiosis in patients with AAA [52]. *Proteobacteria* and *Actinobacteria* are markedly elevated, whereas *Firmicutes* and *Bacteroidetes* are diminished, in patients with AAA [52]. Metabolic detection has further indicated that patients with AAA have low levels of beneficial metabolites and significantly elevated LPS levels [52]. Detailed exploration of the gut microbiota has also been conducted in an Ang II-induced AAA mouse model. *Akkermansia* is considered an important participant, and *Akkermansia* enrichment is negatively associated with AAA diameter [52]. Consistently, network analysis has suggested that *Bacteroidetes* tightly correlates with AAA progression [53]. However, no direct evidence has shown a causal relationship between *Bacteroidetes* and AAA, and this potential relationship must be validated in future work.

Recently, several studies have evaluated the effects of the gut microbiota on AAA progression. Reduction of the gut microbiota by oral antibiotic treatment markedly delays AAA expansion and rupture, thus suggesting a relationship between AAA and the gut microbiota [53]. These beneficial effects are accompanied by a decrease in mobilization of monocytes from spleen, and gut microbiota-derived factors, such as Nod1 ligands, have been suggested to maintain splenic monocytes [54]. In AAA, as in atherosclerosis, TMAO has been suggested to be a crucial mediator facilitating disease progression [55]. Disrupting the production of TMAO by antibiotics, inhibitors, or genetic ablation alleviates AAA progression, even that of established AAA [55]. A mechanistic study has suggested that increased TMAO promotes endoplasmic reticulum stress and apoptosis in VSMCs [55]. The results of delaying establishment of AAA in mice might extend to patients diagnosed with AAA. Studies have estimated the overall effects of the gut microbiota. Interestingly, Tian's comprehensive work has indicated that supplementation with *R. Intestinalis* decreases $CaCl_2$-induced AAA expansion, thus suggesting promising application potential for *R. Intestinalis* in chronic AAA management (Figure 1) [52]. Butyrate, a metabolite of *R. Intestinalis* accounts for the decrease in neutrophil infiltration and neutrophil extracellular trap formation in aneurysmal tissues, in a NOX-dependent manner [52]. Application of *R. Intestinalis* or butyrate in the clinical management of AAA should be further explored, including its safety and convenience. Dosages will also be an important part of developing *R. Intestinalis* therapies.

Intracranial aneurysm (IA) is the localized dilation of blood vessels in the brain, and IA rupture is a life-threatening condition for patients [56]. Recently, the relationship between IA and the gut microbiota has gained increasing attention. Shikata's report first suggested that oral antibiotic administration markedly decreases IA incidence in a murine model, even if the antibiotic administration is stopped before IA induction [57]. Pathological observations have revealed that macrophage infiltration is significantly decreased, and inflammatory cytokines including IL-1β, IL-6, and TNF-α synchronously decline [57]. Furthermore, a metagenome-wide association study of fecal samples from patients with IA has identified that *Bacteroides*, *Parabacteroides*, *Ruminococcus*, and *Blautiawere* are relatively enriched, and transplantation of fecal samples from patients with IA facilitates aneurysm progression in murine models [58]. Analyses including metabolic profiling have suggested a low abundance of *Hungatella hatheway* and diminished circulating taurine levels in both patients with IA and mouse models [58]. Promisingly, oral *Hungatella hatheway* treatment alleviates IA progression and rupture, and is accompanied by elevated taurine levels [58]. These protective effects are mimicked by taurine addition, thus indicating that the *Hungatella hatheway*-taurine pathway is crucial in IA development [58]. *Hungatella hatheway* or taurine supplementation might become a feasible IA intervention. Another species of gut microbiota, *Campylobacter*, is highly elevated in patients with ruptured IA, compared with stable IA [59]. A recent Mendelian randomization study conducted by Ma has demonstrated that *Streptococcus*, *Adlercreutzia*, *Clostridia*, *Rhodospirillaceae*, *Sutterella*, *Victivallis*, and *Peptostreptococcaceae* tend to promote IA, whereas *Oscillospira* and *Paraprevotella* have opposite roles [60]. Nevertheless, the causal relationship and exact mechanisms remain unclear, and animal studies and mechanistic explorations will be required in the future.

The pathogenesis of moyamoya disease (MMD), another relatively rare intracranial artery disease, has not been thoroughly elucidated [61]. Recent studies have correlated MMD with gut microbiota alterations, although the results have been inconsistent. A 16S-sequencing study has revealed elevated *Ruminococcus gnavus* in 27 patients with MMD—a finding associated with elevated risk [62]. However, Takayanagi's work has shown more compelling differences in the oral microbiota than the gut microbiota, in 16 patients with MMD compared with 15 controls [63]. A comprehensive case-control investigation including 60 patients with MMD and 60 controls [64] has observed a marked elevation in *Fusobacteriota* and a marked decline in Actinobacteria in patients with MMD, at the phylum level. Further analysis has indicated that *Lachnoclostridium* and *Fusobacterium* are abundant, and *Bifidobacterium* and *Enterobacter* are diminished in patients with MMD [64]. By combining these four genera, the authors have developed a promising predictive model to stratify patients with MMD [64]. In contrast to previous findings, *Ruminococcus gnavus* and *Peptostreptococcaceae* were not elevated in patients with MMD, and *Peptostreptococcaceae* was even higher in controls. These discrepancies might stem from differences in sample sizes, geographic origins, and analytic methods across studies. Multicenter cohorts of patients with MMD will be indispensable to overcome these limitations. Whether these alterations in the gut microbiota affect the progression of MMD remains undetermined.

## Vasculitis

Vasculitis is a group of autoimmune diseases causing persistent vascular inflammation and injury [65]. Although the exact etiology of vasculitis remains unclear, environmental factors such as the gut microbiota are important triggers of pathogenesis [65, 66]. Kawasaki disease (KD), an acute febrile disease characterized by destruction of small and mid-sized arteries, is the leading cause of acquired heart disease in children [65, 67]. The interplay between the gut microbiota and KD has gradually been revealed [65, 68]. Microbial diversity has consistently been found to be diminished in patients with KD in various studies, although the alterations in the gut microbiota have varied, partially because of differences in study populations and methods [67, 69, 70]. Notably, *Enterococcus* and *Helicobacter* were positively associated with IL-6 levels in patients with KD, and *Fusobacteria*, *Shigella*, and *Streptococcus* were positively with KD activity [67, 71]. Recently, Wang's data have revealed that gut microbiota producing SCFAs are significantly diminished in KD model mice [68]. Intriguingly, administration of *Clostridium butyricum* enriches SCFA-producing bacteria and abolishes the progression of KD, and is accompanied by decreases in IL-1β and IL-6, and maintenance of intestinal barrier integrity [68]. Mechanistic explorations have further demonstrated that butyrate, but not other SCFAs, contribute to the protective effects through elevated phosphatase MKP-1 and downregulated MAPK pathways [68]. Rebalanced Th17s/Tregs are another potential mechanism in the regulation of KD by SCFAs [72]. These studies have provided evidence of application of the probiotic *Clostridium butyricum* in children with KD to minimize KD complications such as coronary artery aneurysms. Clinical trials will be the next step in comprehensively evaluating the effects and safety of this intervention.

## Potential Therapy Targeting the Gut Microbiota and Metabolites

Accumulating evidence indicates crosstalk between the gut microbiota and vascular dysfunction, thus extending the scope of therapy for atherosclerosis, aneurysm, and VC (Table 1) [73, 74]. Dietary modulation is a viable and acceptable means of decreasing chronic vascular inflammation [3, 15]. Specifically, the abovementioned natural products show powerful anti-inflammatory effects with minimal adverse effects [25]. According to high throughput sequencing and animal studies, direct intake of probiotics effectively inhibits atherosclerotic progression [75, 76]. However, the dosages and safety of these treatments should be further evaluated in clinical settings. Clinical evidence of probiotic treatment for VC and aneurysms remains limited. Fecal microbiota transplantation (FMT) has also gained extensive attention and is already used in the treatment of

**Table 1** Recent Findings in Links between the Gut Microbiota and Vascular Disease, from a Translational Perspective.

| Vascular dysfunction | Functional gut microbiota | Functional metabolites | Intervention and causal relationship | Mechanisms | Refs |
|---|---|---|---|---|---|
| Atherosclerosis | - | Propionate | 200 mg/kg in *Apoe*$^{-/-}$ mice; 500 mg twice daily in patients; atherosclerosis decreased | Tregs IL-10 increased; Npc1l1 decreased | [19] |
| Atherosclerosis | *Clostridium* and *Peptostreptococcus* decreased | Indole-3-propionic acid decreased | 50 mg/kg in *ApoE*$^{-/-}$ mice; atherosclerosis decreased | Macrophage reverse cholesterol transport increased; SPI1/miR-142-5p/ABCA1 pathway decreased | [22] |
| Atherosclerosis | - | TMAO increased | Berberine 100 mg/kg/d, 200 mg/kg/d in HFD-induced hamsters; oral berberine 0.5 g twice daily in patients; atherosclerosis decreased | Choline-TMA-TMAO production decreased | [26] |
| Vascular calcification | *Akkermansia* decreased | Propionate decreased | 1 g/kg in VDN-treated rats; calcification decreased | Intestinal barrier function increased; TNF-α IL-1β, and IL-6 decreased | [43] |
| Vascular calcification | - | Butyrate | 1000 mg/kg/day in vitamin D3-induced mice; calcification increased | NF-κB, Wnt, and Akt signaling increased; HDAC expression decreased | [44] |
| Abdominal aortic aneurysm | *R. Intestinalis* decreased | Butyrate decreased | *R. Intestinalis* ($1 \times 10^9$ CFUs/ mouse) or butyrate (400 mg/kg/day) in $CaCl_2$-induced AAA mice; AAA decreased | Neutrophil infiltration and NOX2-dependent neutrophil extracellular trap formation decreased; LPS, TNF-α, IL-1β, IL-6, and MCP-1 decreased; synthetic phenotype changes in VSMCs decreased | [52] |
| Abdominal aortic aneurysm | - | TMAO increased | Ang II and elastase induced AAA models treated with antibiotics, TMAO inhibitor, or FMO3 genetic ablation; AAA decreased | Endoplasmic reticulum stress decreased; VSMC apoptosis decreased | [55] |
| Intracranial aneurysms | *Hungatella hathewayi* decreased | Taurine decreased | *Hungatella hathewayi* $1 \times 10^9$ CFU/ mouse in IA induction surgery; IA decreased | MMP-2 and MMP-9 decreased; VSMC apoptosis decreased | [58] |
| Kawasaki disease | SCFA-producing bacteria decreased | Butyrate, acetate, and propionate decreased | *Clostridium butyricum* ($5 \times 10^6$ CFU/g) in CAWS-induced KD mice; KD decreased | IL-1β and IL-6 decreased; intestinal barrier integrity maintained; phosphatase MKP-1 increased | [68, 72] |

*Clostridium difficile* infection [77]. FMT is has been adequately demonstrated to be involved in vascular atherosclerosis, but has not been used in patients under long-term administration [78, 79]. The FMT process carries a high risk of transplanting other pathogenic microorganisms. Given that metabolites such as TMAO profoundly damage vascular walls, the development of selective TMAO inhibitors is another direction for protecting cardiac health [80, 81]. Elucidation of the interaction between the gut microbiota and vascular disease has helped develop new therapies for the management of atherosclerosis, aneurysm, and VC.

## Conclusion and Outlook

Emerging investigations have strongly correlated gut microbiota dysbiosis and vascular dysfunction, including atherosclerosis, aneurysms, and VC. Alterations in the gut microbiota and metabolites, and their functions, have been partially clarified through the use of sequencing technologies and bioinformatics analysis. The causal relationships between these alterations and vascular pathogenesis remain unclear. A paucity of human studies have explored signaling pathways. Given the complexity of the gut microbiota and diverse metabolites, more comprehensive research is warranted to deepen understanding of the crosstalk between the gut microbiota and host under physiological and pathological conditions. Mechanistic animal studies are also necessary. Recently, several encouraging results have identified targeted species and metabolites. Translational studies including clinical trials should be conducted to better manage vascular diseases. Dietary therapy is considered a viable and acceptable strategy to modify the gut microbiota and minimize adverse vascular events. Long-term effects and safety should be a focus of future work.

Emerging artificial intelligence technology has been applied to establish diagnostic tools for early screening, personalized diagnosis, and risk stratification for cardiovascular diseases [82]. Analysis of the gut microbiota provides extensive information on the development of vascular disease, and the gut microbiota is anticipated to be integrated into current artificial intelligence tools to enrich understanding of vascular diseases [83], with far-reaching clinical implications.

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## Conflict of Interest

The authors declare they have no conflicts of interest.

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