RESEARCH PAPER

The Gut Microbiota Metabolite TMAO in Abdominal Aortic Aneurysm: Advances in Pathogenesis, Prevention, and Treatment

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Received: 18th Dec, 2025; Revised: 11th Feb 2026; Accepted: 17th Feb, 2026; Available Online: 30th March, 2026

ABSTRACT

Abdominal aortic aneurysm (AAA) is a life-threatening vascular disease lacking targeted pharmacological therapies. Emerging evidence highlights the gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) as a core driver of AAA pathogenesis. This review systematically summarizes how disrupted TMAO homeostasis accelerates AAA progression. Specifically, TMAO amplifies local vascular inflammation and oxidative stress, induces vascular smooth muscle cell (VSMC) senescence, accelerates extracellular matrix (ECM) degradation, and promotes intraluminal thrombus (ILT) formation. Furthermore, we explore promising therapeutic strategies targeting the gut-TMAO axis, including probiotics and prebiotics, specific enzyme inhibitors, and traditional Chinese medicine (TCM). Finally, we discuss current clinical translation challenges, such as inter-individual microbiome heterogeneity. Addressing these hurdles through precision medicine and large-scale clinical trials will be crucial for developing novel, non-surgical treatments for AAA.

Keywords: *Abdominal aortic aneurysm; Trimethylamine N-oxide; Gut microbiota; Gut-vascular axis; Pathogenesis; Treatment*

How to cite this article: Kang T and Ismail NA, The Gut Microbiota Metabolite TMAO in Abdominal Aortic Aneurysm: Advances in Pathogenesis, Prevention, and Treatment. Int J Drug Deliv Technol. 2026;16(3): 340-348. DOI: 10.25258/ijddt.16.3.38

Source of support: Nil.

Conflict of interest: None

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1. INTRODUCTION

Abdominal aortic aneurysm (AAA) is a chronic, life-threatening vascular disease. Its main features are permanent local dilation and structural remodeling of the abdominal aortic wall. Often described as a "time bomb" in cardiovascular medicine, a ruptured AAA carries a mortality rate of over 80%. Worldwide, these ruptures account for 150,000 to 200,000 deaths annually(Cai & Chen, 2025; Qian et al., 2022). Several core pathological processes drive AAA. These include chronic inflammatory infiltration within the vessel wall, alongside the apoptosis, senescence, and phenotypic switching of vascular smooth muscle cells (VSMCs). The disease is also marked by elastin fragmentation, pathological remodeling of the extracellular matrix (ECM), adventitial neovascularization, and increased local and systemic oxidative stress(Shi et al., 2025a; Stepien et al., 2022). Open surgical repair and endovascular aneurysm repair (EVAR) are currently highly effective at preventing large aneurysms from rupturing. However, clinical practice still lacks targeted drug therapies to stop small and medium-sized aneurysms from expanding in their early stages. Traditional risk factors like advanced age, male sex, smoking, hypertension, and severe atherosclerosis are strongly linked to AAA. Yet, these factors alone cannot fully explain the complex biological mechanisms behind the disease. Finding novel pathogenic targets and non-surgical treatments remains a pressing clinical need.

Recent advances in high-throughput sequencing, multi-omics, and microecology have introduced the "gut-vascular/heart axis" theory. This concept provides a fresh way to understand how cardiovascular diseases develop. Researchers now view the gut microbiome as a massive internal endocrine organ. The metabolites it produces can enter the host's bloodstream, act as signaling molecules, and profoundly affect distant target organs.

One gut-derived metabolite in particular has gained significant scientific attention: trimethylamine N-oxide (TMAO). TMAO is the end product of a specific metabolic chain. It begins when gut bacteria break down dietary precursors like choline and L-carnitine, which are common in red meat and eggs. The resulting intermediate is then oxidized by flavin-containing monooxygenase 3 (FMO3) in the liver to form TMAO(Luqman et al., 2024). Extensive research shows that TMAO is an independent risk factor for various cardiovascular conditions, including atherosclerosis, heart failure, and hypertension. More recently, studies have clearly linked disrupted TMAO homeostasis to the onset, progression, and rupture risk of AAA(Cameron et al., 2025).

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This review systematically outlines how gut dysbiosis and TMAO contribute to the underlying pathology of AAA. We examine the molecular networks through which TMAO drives local vascular inflammation, induces VSMC senescence, accelerates matrix degradation, and disrupts macrophage reverse cholesterol transport. Finally, we summarize potential prevention and treatment strategies targeting the gut microbiota-TMAO axis. These approaches include probiotic and prebiotic supplementation, TMAO production inhibitors, and traditional Chinese medicine interventions. By doing so, we hope to provide a comprehensive reference and fresh perspectives for early diagnosis, mechanistic studies, and the discovery of non-surgical treatments for AAA.

2. THE FORMATION OF THE GUT MICROBIOTA-TMAO METABOLIC AXIS AND ITS LINK TO ABDOMINAL AORTIC ANEURYSM

2.1 Gut Microbiota Dysbiosis and AAA

Substantial experimental evidence links the gut microbiome to cardiovascular pathophysiology, highlighting its major role in the development of AAA. Profound shifts in gut microbiota composition—manifesting as microbial dysbiosis—have been consistently observed across diverse AAA animal models, including angiotensin II (Ang II)-induced, elastase perfusion, and erythropoietin (EPO)-induced models. Specifically, the abundance of certain beneficial taxa (such as Akkermansia muciniphila and Lactobacillus) is markedly depleted, whereas several inflammation-associated pathogenic or opportunistic genera (including Oscillospira, Coprococcus, and Faecalibacterium prausnitzii) exhibit a concomitant enrichment in AAA groups (Chui et al., 2024; S. Liu et al., 2022). Bacterial network analysis suggests that the phylum Bacteroidota might hold a dominant position as AAA forms, acting as a primary bacterial group regulating the structure and function of the abdominal aorta (Xiao et al., 2023; Xie et al., 2020). This bacterial imbalance can damage the mechanical barrier of the intestinal mucosa and increase gut permeability. As a result, bacterial components like lipopolysaccharide (LPS) can leak into the bloodstream, activating signaling pathways such as Toll-like receptor 4 (TLR4) and nuclear factor kappa-B (NF-κB) (Di Vincenzo et al., 2024; Ghosh et al., 2020). This sequence of events triggers a systemic inflammatory response and creates an inflammatory amplification loop within the local vessel wall. This loop prompts the heavy release of chemokines and pro-inflammatory cytokines (such as IL-6 and TNF-α), which then drive macrophage infiltration and upregulate the expression of matrix metalloproteinases (MMPs), leading to the pathological breakdown of the ECM. Together, these processes lay the groundwork for the continuous expansion of the AAA (An et al., 2022; Tian et al., 2022). However, beyond the direct stimulation by bacterial components like LPS, the bridging role of specific microbial metabolites—especially TMAO—in AAA pathogenesis is gaining increasing attention.

2.2 Biosynthesis and Homeostasis of TMAO

The production of TMAO is highly dependent on the co-metabolism of the "gut microbiota-host liver" axis. It mainly originates from foods rich in specific dietary precursors, including choline, phosphatidylcholine, and L-carnitine (Caradonna et al., 2025). In the gut, specific bacteria use lyase enzymes to break these precursors down into trimethylamine (TMA). The TMA then travels through the portal vein to the liver, where the enzyme FMO3 oxidizes it to form the final product, TMAO (Caradonna et al., 2025; Gątarek & Kałużna-Czaplińska, 2021). Several factors control the steady levels of TMAO in the body, including diet, microbiome composition, liver and kidney function, age, and medical treatments. For instance, declining kidney function can reduce TMAO excretion, causing an abnormal spike in its blood plasma levels; conversely, antibiotics, probiotics, or specific dietary interventions can alter the abundance of TMA-producing bacteria, reshaping TMAO production directly at the source (Jang et al., 2024). It is precisely the dysregulation of this "gut-liver" metabolic axis that allows abnormally elevated TMAO to enter the bloodstream and act upon the vascular wall, thereby deeply participating in the aforementioned pathological progression of AAA.

3. MOLECULAR MECHANISMS OF TMAO IN PROMOTING THE PATHOGENESIS OF AAA

As a key end-product of gut microbiota metabolism, the pathogenic role of TMAO in cardiovascular diseases has been widely reported. Recently, extensive evidence from animal models and clinical cohorts has confirmed that elevated TMAO levels are significantly positively correlated with AAA incidence, maximum aortic diameter, and rupture risk (Benson et al., 2023; Wei et al., 2024). Based on current evidence, TMAO primarily drives the pathological progression of AAA through four core pathways: amplifying vascular inflammation and oxidative stress, inducing vascular smooth muscle cell (VSMC) dysfunction and ECM degradation, disrupting lipid metabolism, and enhancing pro-thrombotic tendencies (Figure 1).

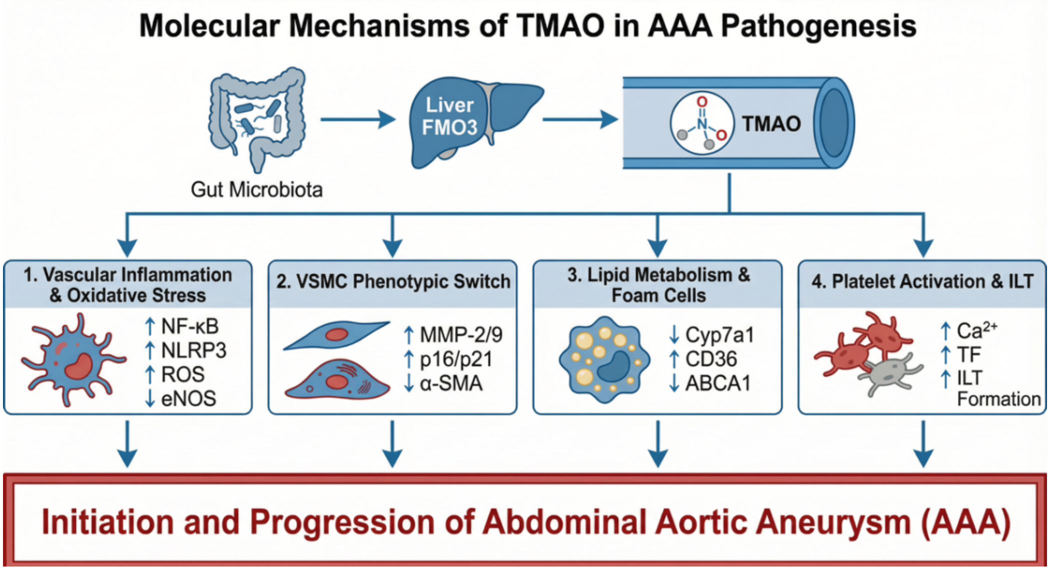

Figure 1: Molecular mechanisms of TMAO in AAA pathogenesis

3.1 Promoting Vascular Inflammation and Endothelial Oxidative Stress

TMAO significantly amplifies the inflammatory and oxidative stress microenvironment within the vascular endothelium and smooth muscle. Regarding inflammatory networks, TMAO activates classical signaling pathways such as nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK). This upregulates the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), thereby enhancing the adhesion and infiltration of monocytes/macrophages into the vessel wall (Y. Liu & Dai, 2020; Wei et al., 2024). In terms of oxidative stress, TMAO not only directly activates the ROS-TXNIP-NLRP3 inflammasome but also inhibits the protective SIRT1/SIRT3-SOD2 pathway, triggering a massive accumulation of mitochondrial reactive oxygen species (ROS). This high oxidative burden reduces endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) production, leading to severe endothelial-dependent vasodilation dysfunction (Shanmugham et al., 2023; Sun et al., 2016). Furthermore, under high TMAO exposure, the p53/p21 senescence pathway is activated in vascular cells, leading to a surge in the secretion of pro-inflammatory cytokines (such as TNF-α and IL-1β), which further exacerbates vascular aging and functional decline (Hu et al., 2022; Saaoud et al., 2023).

3.2 Inducing VSMC Phenotypic Switching, Senescence, and ECM Degradation

VSMCs play a decisive role in maintaining the structural integrity of the aortic wall, and TMAO is a key driver in breaching this defense. First, TMAO induces a phenotypic switch in VSMCs from a normal "contractile phenotype" to a pathological "synthetic phenotype," characterized by a decrease in contractile markers (e.g., α-SMA) and a significant increase in synthetic markers (e.g., Osteopontin) (Wei et al., 2024). Studies suggest this process may involve mechanisms similar to the inhibited Axl signaling observed in thoracic aortic aneurysms (Leng et al., 2025). Second, stimulated by TMAO-induced high ROS levels and enhanced p16/p21 signaling, VSMCs exhibit pronounced premature senescence and apoptosis (Hu et al., 2022; Shi et al., 2025b). Most critically, TMAO directly upregulates the expression and activity of MMPs (particularly MMP-2 and MMP-9) in macrophages and VSMCs. This accelerates the pathological degradation of elastic fibers and collagen in the aortic wall, directly weakening its load-bearing structure and laying the groundwork for aneurysm expansion and elastic lamina rupture (Benson et al., 2023; Zhou et al., 2022).

3.3 Disrupting Lipid Metabolism and Reverse Cholesterol Transport

Beyond directly mediating local vascular wall damage, TMAO acts as "pathological fuel" for AAA by interfering with systemic lipid metabolism networks. In the liver, TMAO inhibits cholesterol 7α-hydroxylase (CYP7A1) and activates the FXR/SHP pathway. This significantly suppresses the conversion of cholesterol into bile acids and alters the bile acid profile, leading to hyperlipidemia (Ding et al., 2018; Pathak et al., 2020). Locally in vascular macrophages, TMAO not only upregulates scavenger receptors like CD36 and SR-A1 to increase lipid uptake but also inhibits the expression of adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1). This hinders the reverse cholesterol transport (RCT) process and accelerates foam cell formation (Canyelles et al., 2018; Y. Liu & Dai, 2020; Zhen et al., 2023). Given that severe atherosclerosis is a major comorbidity and pathological basis of AAA, this systemic lipid burden and local foam cell accumulation mediated by TMAO undoubtedly fuel the chronic inflammation and remodeling of the AAA vessel wall (Abudureheman et al., 2025).

3.4 Pro-thrombotic Tendency and Intraluminal Thrombus (ILT) Formation

Recent population-based cohorts have revealed a strong association between TMAO levels and arterial thrombotic events (Witkowski et al., 2022). In vitro and in mouse models, pathological concentrations of TMAO enhance calcium (Ca^{2+}) mobilization and the phosphorylation of MAPK (ERK1/2, JNK) pathways in platelets, leading to platelet hyperreactivity (Y. Liu & Dai, 2020; Shanmugham et al., 2023). Simultaneously, TMAO upregulates the expression of endothelial tissue factor (TF), significantly increasing the thrombus burden in injured arteries (a pro-thrombotic effect that can be reversed by inhibiting TF or using gut TMA-lyase inhibitors) (Witkowski et al., 2022; Zhou et al., 2022). In the pathological progression of AAA, the ubiquitous ILT serves as a "reservoir" that traps and releases proteases and inflammatory mediators. The hypercoagulable state induced by TMAO is highly likely to promote the continuous formation and expansion of ILT, causing it to steadily deliver MMPs and cytokines to the underlying vessel wall, accelerating its destruction (Benson et al., 2023; Witkowski et al., 2022). This vicious cycle of "TMAO - Thrombosis - ILT - Wall Destruction" is emerging as a highly promising new research hotspot in AAA pathogenesis.

4. PREVENTION AND TREATMENT STRATEGIES TARGETING THE TMAO-GUT MICROBIOTA AXIS IN AAA

Given the core driving role of TMAO in the pathogenesis of AAA, modulating the gut microecology to intervene in the TMAO metabolic axis has emerged as a highly promising strategy for preventing and treating the disease. Current preclinical and translational research mainly focuses on three areas of intervention (Figure 2):

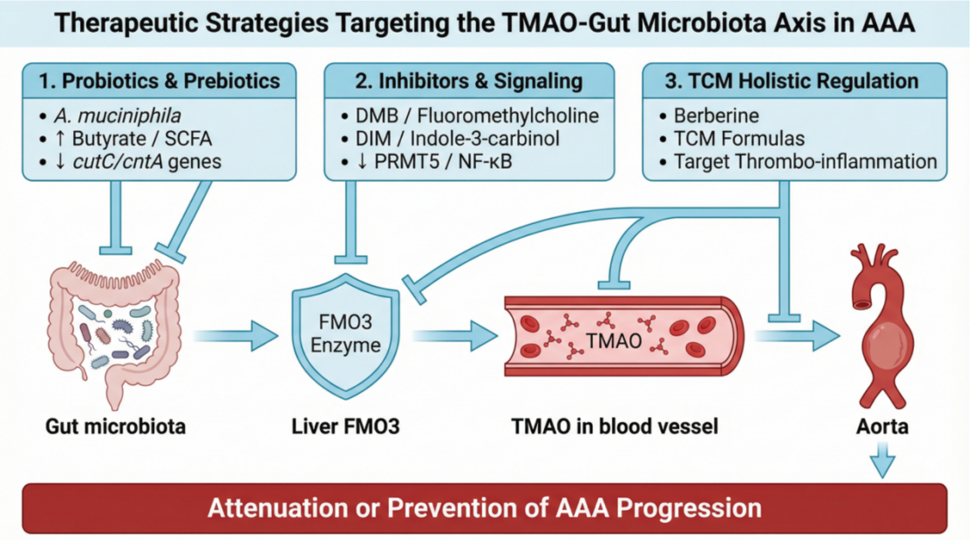

Figure 2: Therapeutic strategies targeting the TMAO-Gut Microbiota Axis in AAA

4.1 Probiotics and Prebiotics: Reshaping Microecology to Reduce TMAO Burden

Several studies show that supplementing with probiotics and prebiotics can significantly improve gut dysbiosis, thereby blocking the TMAO generation cascade from the source. In mouse models of AAA, oral administration of Akkermansia muciniphila not only restores bacterial α-diversity but also directly downregulates the expression of TMA-producing lyase genes (such as cutC/cntA/yeaW/X), lowering serum TMA/TMAO levels (He et al., 2022; Wan et al., 2025). At the same time, this strain lowers the expression of MMP-1/9 and various inflammatory factors (IL-6, IFN-γ, CRP), significantly inhibiting aneurysm formation and aortic structural damage (S. Wang et al., 2024). Additionally, specific prebiotics promote the growth of butyrate-producing bacteria (such as Ruminococcus intestinalis), increasing the generation of short-chain fatty acids (SCFAs), particularly butyrate. Butyrate not only improves gut mucosal barrier function and reduces the blood concentration of pro-inflammatory substances like LPS, but also reduces the formation of neutrophil extracellular traps (NETs) and abnormal VSMC phenotypes, effectively easing local inflammation and pathological remodeling of the vascular wall (Du et al., 2024; P. Liu et al., 2021; Mann et al., 2024; Venegas et al., 2019).

4.2 TMAO Production Inhibitors and Downstream Pathway Interventions

Researchers have explored various chemical inhibitors targeting the TMAO production process and its downstream signals. First, inhibiting gut TMA lyase is an effective way to control TMAO generation. One classic TMA inhibitor is 3,3-dimethyl-1-butanol (DMB). It significantly lowers plasma TMAO levels, which improves vascular endothelial function and reduces ROS production (Chen et al., 2023; Restini et al., 2021). In recent AAA models, novel choline TMA lyase inhibitors (such as fluoromethylcholine) have shown more thorough inhibitory efficacy, nearly clearing TMAO from the blood and effectively delaying AAA progression (Benson et al., 2023). Second, targeting liver FMO3 is another important strategy. Inhibitors like 3,3'-diindolylmethane (DIM) and indole-3-carbinol can effectively block the TMA-to-TMAO conversion, significantly reducing maximum aortic diameter and vascular lesion burden (Benson et al., 2023; Oktaviono et al., 2023; Shanmugham et al., 2023). Finally, intervening in signaling pathways induced by TMAO also shows clear therapeutic potential. For instance, protein arginine methyltransferase 5 (PRMT5) plays a vital part in the TMAO-dependent Nox4–PRMT5–NF-κB inflammatory axis. Using PRMT5 inhibitors or gene knockout technology can effectively reduce VCAM-1 expression and macrophage adhesion (H. Liu et al., 2022). Meanwhile, natural polyphenols (like nobiletin) can weaken TMAO-induced MAPK activation and endothelial injury (Yang et al., 2019). Furthermore, upregulating RCT key proteins (CYP7A1, ABCA1/ABCG1) can enhance cholesterol efflux, indirectly reducing the adverse effects of TMAO on atherosclerosis and vascular remodeling (Z. Li et al., 2022; Nyandwi et al., 2021; Shanmugham et al., 2023).

4.3 Traditional Chinese Medicine Regulating Gut Microbiota and TMAO: Multi-Target Holistic Intervention

Recently, the use of traditional Chinese medicine (TCM) for microecological regulation has attracted widespread attention. Its "multi-target, holistic regulation" approach offers a new idea for the conservative treatment of AAA. For example, the classic cardiovascular TCM monomer Berberine has been shown to have a dual inhibitory effect: on the one hand, it reshapes the microbiota, reduces the abundance of TMA-producing bacteria with cutC/cntA genes, and directly inhibits TMA production (X. Li et al., 2021; Ma et al., 2022). On the other hand, it downregulates liver FMO3 expression, synergistically reducing the conversion of TMA to TMAO (Z. Wang et al., 2022; Zhu et al., 2020). In high-choline/high-fat diet and Ang II models, oral Berberine significantly lowers plasma TMA/TMAO, improving blood pressure, endothelial function, and vascular remodeling (Ma et al., 2022; Z. Wang et al., 2022). Meanwhile, TCM formulas (such as the Tongmai Zhuyu decoction) effectively improve low-grade inflammation and lipid metabolism disorders by reshaping the entire gut microbiota (Ji et al., 2020). Furthermore, various TCMs inhibit excessive platelet activation, coagulation cascades, and thrombo-inflammation without increasing bleeding risks (Su et al., 2024; Xu et al., 2025). This provides a highly translatable candidate strategy for blocking the ILT-related pathological cascade, which is critical in AAA progression. Although direct clinical trials of TCM targeting TMAO in AAA patients are still lacking, these strategies hold great clinical prospects due to the highly overlapping "gut-vascular axis" mechanisms between AAA and atherosclerosis.

4.4 Summary

In summary, reshaping the microecology with probiotics/prebiotics, using TMA/TMAO production inhibitors and downstream signal blockers, and the multi-target holistic regulation of TCM collectively form the framework for AAA prevention and treatment targeting the TMAO-gut microbiota axis. Although current evidence relies mainly on animal experiments and early clinical data, the therapeutic prospects are very optimistic.

However, high-quality randomized controlled trials (RCTs) are still needed in the future to rigorously verify intervention dosages, long-term safety, and clinical endpoint benefits.

5. CLINICAL TRANSLATION CHALLENGES AND FUTURE PROSPECTS

Extensive basic and animal data support the important role of TMAO and gut microbiota in the pathogenesis of AAA. However, translating these findings into clinical practice still faces many challenges. These mainly include the following areas:

5.1 Inter-individual Microbiome Heterogeneity

Human gut microecology is heavily influenced by highly individualized factors. These include genetic background, regional diets, and lifestyle. As a result, response rates to the same probiotic or metabolic intervention vary vastly among different patients. Future approaches will need to rely on technologies such as metagenomics. This will help to establish precise intervention protocols based on an individual patient's microbiome profile.

5.2 The Interactive Effects of TMAO and Other Risk Factors

Beyond TMAO, inflammation, oxidative stress, hyperlipidemia, and abnormal blood pressure are also major risk factors for AAA. Drug interventions in clinical trials often fail to target all these pathogenic pathways at once. This leads to poor outcomes for single-drug therapies. Therefore, researchers urgently need to develop multi-target and combination treatment strategies.

5.3 Limitations of Current Clinical Trials

Most current clinical data show a dose-dependent positive correlation between TMAO levels and cardiovascular events. However, some drug trials have failed to significantly improve clinical outcomes. This suggests a gap between the biological significance of TMAO and its actual clinical effect. Future research must design better, larger-scale RCTs. These trials are needed to verify whether adjusting TMAO levels can truly prevent or delay the progression of AAA.

5.4 Safety and Long-term Efficacy Issues

Long-term inhibition of TMAO synthesis or the alteration of gut microbiota may affect other physiological processes in the body. In certain situations, TMAO actually offers protective effects. It helps stabilise protein structures and regulates osmotic pressure. Therefore, future drug development faces a distinct challenge. Researchers must find ways to reduce the pathogenic effects of TMAO without disrupting its potential physiological functions.

5.5 The Translational Gap Between Animal Models and Humans

Animal experiments have provided extensive mechanistic evidence. However, significant differences exist in gut bacterial composition and metabolic levels between humans and rodents. These differences make it difficult to directly apply the intervention effects seen in animal models to clinical practice. Furthermore, there is still a lack of large-scale, multi-center, and cross-ethnic clinical data in humans. This shortage continues to limit the progress of translational applications.

5.6 Future Research Directions and Prospects

In summary, to overcome the aforementioned translational challenges, future research should focus on several key areas. First, researchers should conduct integrated analyses using multi-omics approaches. These include the microbiome, metabolome, and transcriptome. This will help to fully understand the global network through which TMAO and gut bacteria mediate the pathogenesis of AAA. Second, there is a need to develop individualized precision medicine strategies. These would offer personalised intervention plans based on a patient's bacterial composition and metabolic state.

Third, studies should explore multi-target combination therapies. Examples include combining probiotics, TMAO inhibitors, and anti-inflammatory drugs. Finally, strengthening interdisciplinary collaboration will be vital. This will ensure the successful translation of basic research into clinical practice.

6. CONCLUSION

Recent studies clearly show how gut dysbiosis and its signature metabolite, TMAO, drive the onset and progression of AAA. TMAO amplifies both local and systemic vascular inflammation. It triggers severe oxidative stress, drives VSMC dysfunction, and accelerates ECM degradation. It also disrupts global lipid metabolism. Through these combined actions, TMAO fuels multiple pathological stages of AAA.

Targeting the gut microbiota-TMAO axis offers a fresh approach to preventing and treating the disease. This is particularly valuable given the current lack of effective drug therapies. Potential interventions include prebiotics, specific enzyme inhibitors, and TCM preparations.

However, moving these strategies into everyday clinical practice still faces several hurdles. Researchers must confirm strict causal relationships and address inter-individual heterogeneity. They also need to conduct thorough long-term safety evaluations. Future translational research must be both systematic and rigorous. This work will ultimately decide whether targeting this axis can truly transform the landscape of AAA management.

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