REVIEW ARTICLE

Cardiovascular disease and microbiome: focus on ischemic stroke

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ABSTRACT

Cardiovascular and cerebrovascular diseases, encompassing conditions such as ischemic heart disease and ischemic stroke (IS), remain the leading global cause of death and disability. While traditional cardiovascular risk factors (eg, hypertension, diabetes, and atherosclerosis) are well established, emerging research underscores the critical role of gut microbiota in the development and progression of both cardiac and cerebrovascular events. The microbiota–gut–brain axis is a bidirectional communication system involving neural, immune, and metabolic pathways that link gut microbial activity to vascular and brain function. Dysbiosis, marked by reduced microbial diversity and an imbalance between beneficial and pathogenic taxa, has been associated with systemic inflammation, endothelial dysfunction, increased intestinal permeability, and thrombosis. Microbial metabolites, such as trimethylamine N-oxide (TMAO), short-chain fatty acids, and bile acid derivatives modulate blood–brain barrier integrity, vascular tone, and neuroinflammatory responses. Both cardiovascular and cerebrovascular diseases share key microbiota-related mechanisms, including TMAO-mediated platelet activation and low-grade endotoxemia, although IS is more acutely affected by gut barrier disruption and neuroinflammation. In IS, gut dysbiosis also contributes to poststroke complications, such as hemorrhagic transformation, neuropsychiatric issues, and epilepsy. Advances in sequencing and metabolomics enabled identification of microbial signatures associated with the risk for an acute ischemic event and patient prognosis. Therapeutic strategies targeting the gut microbiota—including dietary interventions, probiotics, prebiotics, and synbiotics, fecal microbiota transplantation, and intestinal epithelial stem cell therapy—show promise in mitigating vascular injury and improving recovery. This narrative review highlights current insights into microbiota-related cardiovascular and cerebrovascular events, with a focus on IS.

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Introduction Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality globally, accounting for more than 612 million new cases and an estimated 19.41 million deaths each year. According to the American Heart Association, in 2021, ischemic heart disease and stroke were the 2 leading causes of cardiovascular deaths globally.[1] Stroke is generally categorized into 2 main types: ischemic stroke (IS) and hemorrhagic stroke, with the latter encompassing both intracerebral and subarachnoid hemorrhages. IS accounts for approximately 80% of all stroke cases worldwide. Among its diverse manifestations, IS is a critical cerebrovascular event characterized by a sudden loss of blood flow to brain tissue, resulting in neurological deficits and potentially long-term disability. Beyond age, sex, and genetic predisposition, several modifiable risk factors, such as elevated body mass index, high fasting blood glucose level, elevated systolic blood pressure, alcohol consumption, smoking, physical inactivity, and renal insufficiency, contribute to an increased risk of IS.[2] In recent years, the gut microbiome has emerged as a novel player in the pathogenesis of cardiovascular and cerebrovascular diseases.[3] The human gut harbors trillions of microorganisms (predominantly bacteria) that engage in complex interactions with the host. The gut microbiome is mainly comprised of 5 major

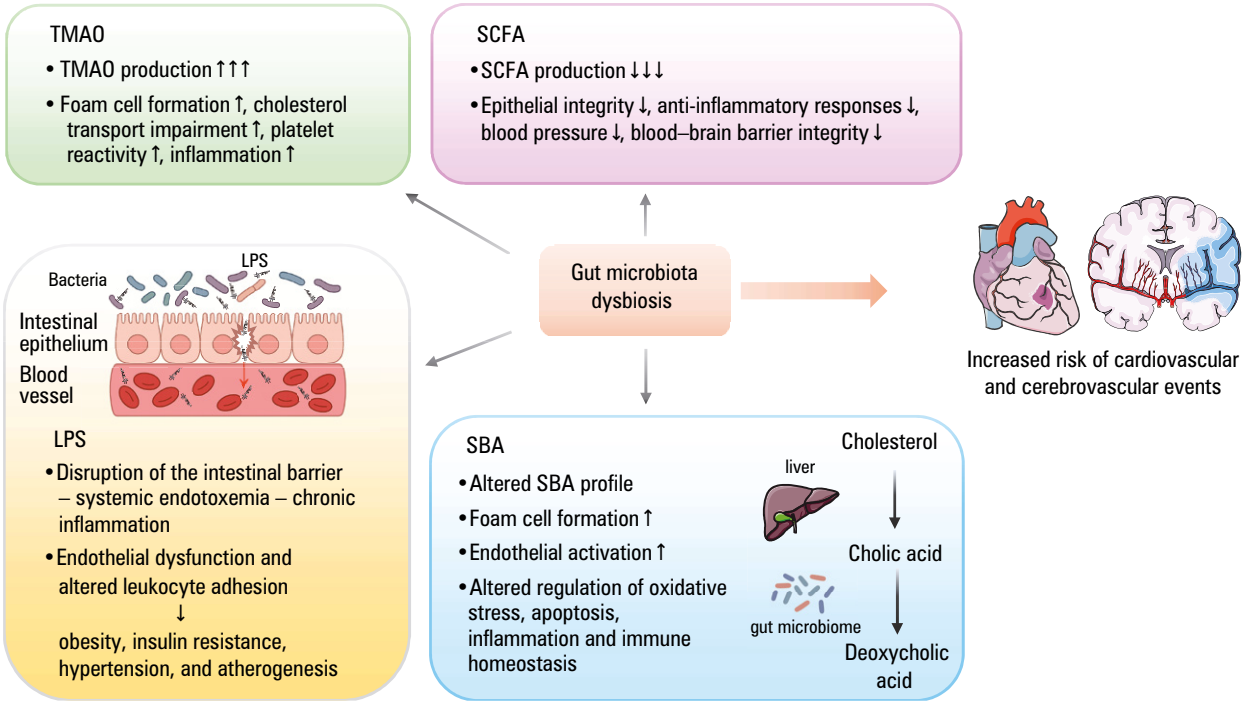

FIGURE 1 Gut microbiota–derived mediators in cardiovascular and neurovascular disease. The Figure summarizes mechanistic pathways through which gut dysbiosis contributes to cardiovascular and cerebrovascular disease. Disrupted microbial composition leads to increased production of proatherogenic metabolites, such as trimethylamine N-oxide (TMAO) and lipopolysaccharide (LPS), promoting systemic inflammation, endothelial dysfunction, and thrombosis. Simultaneously, reduced levels of beneficial short-chain fatty acids (SCFAs) impair the gut and blood–brain barrier integrity, modulate immune responses, and exacerbate vascular dysfunction. Altered bile acid metabolism further influences lipid homeostasis and vascular tone.

Abbreviations: ↓, decrease; ↑, increase; SBA, secondary bile acids

phyla: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia.[4] These microbes contribute to a wide range of physiological processes, including digestion, nutrient absorption, and synthesis of bioactive compounds, and play a crucial role in guiding the development and functional maturation of the immune system.[5] Notably, the composition and function of the gut microbiota are now widely acknowledged as key modulators of systemic inflammation, lipid metabolism, and vascular integrity—critical pathways involved in the pathogenesis of CVD and IS.[6]

This narrative review aims to summarize current knowledge on the intersection of gut microbiota and IS. We discuss the pathophysiological and microbiological mechanisms, clinical associations, and potential therapeutic targets related to the gut microbiome in IS.

The role of gut dysbiosis and microbial metabolites in vascular pathophysiology The gut microbiota plays a crucial role in host physiology, including metabolic regulation, immune homeostasis, and cardiovascular integrity. In recent years, gut dysbiosis has been implicated in the pathogenesis of CVD and neurovascular diseases through multiple interrelated pathways, such as systemic inflammation, metabolic endotoxemia and impaired vascular function, altered lipid metabolism, endothelial dysfunction, and thrombosis.[7] The changes mediated by microbial metabolites caused by dysbiosis are summarized in FIGURE 1.

A hallmark of dysbiosis in cardiometabolic conditions is the altered Firmicutes / Bacteroidetes ratio, along with a reduction in beneficial short-chain fatty acid (SCFA)-producing anaerobes and an increase in gram-negative bacteria that disrupt the intestinal barrier.[8] These factors contribute to increased intestinal permeability, allowing bacterial endotoxins, such as lipopolysaccharide (LPS), to enter the circulation. Once present in the bloodstream, these toxins activate Toll-like receptor 4 (TLR4), expressed on immune (eg, macrophages, dendritic cells) and endothelial cells, thereby promoting chronic inflammation. Elevated LPS levels have been linked to insulin resistance as well as obesity, hypertension, and atherogenesis through mechanisms involving endothelial dysfunction and leukocyte adhesion.[9] Elevated circulating levels of LPS and zonulin, markers of impaired intestinal barrier integrity, have been shown to induce prothrombotic changes by promoting the formation of compact, less lysable fibrin networks and enhancing systemic thrombogenic potential. Increased LPS levels in plasma have also been linked to accelerated thrombin generation, platelet activation, and development of denser fibrin clots, reinforcing the role of endotoxemia-driven coagulation in CVD.[10,11] Overall, dysbiosis-associated endotoxemia provides a mechanistic link between gut leakiness

and thromboembolic events in CVD and cerebrovascular disease. By altering fibrin structure and clot stability, the gut microbiota contributes directly to the prothrombotic milieu.

Another well-studied metabolite is trimethylamine N-oxide (TMAO), which is synthesized in a 2-step process: gut bacteria first convert dietary nutrients (eg, choline, phosphatidylcholine, and L-carnitine) into trimethylamine, which is then oxidized by hepatic flavin–containing monooxygenase 3 to form TMAO.[12] Elevated plasma TMAO levels have been associated with an increased risk of cardiovascular events.[13] Studies have shown that TMAO promotes foam cell formation, impairs cholesterol transport, and enhances platelet reactivity, contributing to plaque formation and thrombosis.[14,15] Inhibition of microbial trimethylamine lyases reduces TMAO levels and atherosclerotic lesion size without disrupting the overall microbiota.[16] Additionally, TMAO activates proinflammatory pathways, such as the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing protein 3 (NLRP3) inflammasome, and alters endothelial nitric oxide synthase function, exacerbating vascular dysfunction.[17]

Conversely, SCFAs—mainly acetate, propionate, and butyrate—serve protective roles. Produced by bacterial fermentation of dietary fibers, SCFAs engage G-protein–coupled receptors (GPR41/43) to enhance epithelial barrier integrity and anti-inflammatory responses, reduce sympathetic activity, and lower blood pressure. They also influence the renin–angiotensin system via olfactory receptors in the kidney.[18,19] Dysbiosis can lead to reduced SCFA production, impaired gut barrier function, and systemic endotoxemia, all of which may exacerbate cardiovascular pathology.[19] High-fiber diets and SCFA supplementation were shown to restore microbial balance and prevent hypertension and heart failure in animal models.[20] In humans, a reduced abundance of SCFA-producing bacteria was associated with hypertension and vascular stiffness.[21] Butyrate additionally supported the blood–brain barrier (BBB) integrity and dampened neuroinflammation after stroke by acting on microglia and enhancing neurotrophic signaling in mice.[22]

Secondary bile acids, modified by gut bacteria from primary bile acids, also influence vascular health through the nuclear farnesoid X receptor (FXR) and the membrane Takeda G protein–coupled receptor 5 (TGR5), affecting lipid metabolism, vascular tone, and inflammation.[23] Dysbiosis alters bile acid composition, thus promoting foam cell formation and endothelial activation.[24] Secondary bile acids exert neuroprotective effects in IS by regulating oxidative stress, apoptosis, inflammation, and immune homeostasis.[25]

Gut–brain axis and ischemic stroke

Gut dysbiosis and microbiota shifts in ischemic stroke The microbiota–gut–brain axis (MGBA) refers to a complex, bidirectional communication network linking the gastrointestinal tract with the central nervous system. It incorporates neural pathways, such as the vagus nerve, hormonal signaling via the hypothalamic–pituitary–adrenal axis, immune signaling pathways, and microbial metabolites. MGBA plays a crucial role in maintaining neurovascular homeostasis.[26] Gut microbes and their metabolic products can influence neuroinflammation, immune activation, and neuronal survival.[27] Conversely, the brain, via the autonomic nervous system, can directly affect gut motility, secretion, and microbiota composition.[28] The gastrointestinal tract contains a majority of immune cells in the body; thus, an IS event induces large-scale migration of these cells to the brain. Stroke-induced disruption of autonomic control often leads to gastrointestinal dysmotility, impaired barrier function, and shifts in microbial populations. These changes can compromise nutrient absorption, increase gut permeability, and potentiate systemic inflammation, thereby establishing a harmful feedback loop that worsens neural injury.[29]

Recent advances in genomics and bioinformatics have facilitated large-scale investigations into the association between gut microbiota and stroke. Mendelian randomization studies, sequencing, and metabolomic profiling have identified specific microbial taxa and metabolites that correlate with stroke risk, severity, and prognosis.[30,31] Stroke models confirm that the microbiota composition influences infarct size and neuroinflammation; recolonization with dysbiotic microbiota worsens outcomes.[32] Following IS, significant changes in the composition and diversity of the gut microbiota occur, and such disruptions may also contribute to the development of stroke itself. Risk factors associated with IS and composition of the gut microbiota are influenced by common conditions, such as diabetes, hypertension, hyperlipidemia, obesity, and vascular dysfunction.[33] A consistent finding across several studies is the reduction / disruption of overall α- and β-diversity in both IS patients and stroke model animals.[34,35] The most prominent poststroke bacterial shift is the overgrowth of Enterobacteriaceae, a family that includes *Escherichia coli*, the abundance of which increases notably during IS. Such an overgrowth has been confirmed in both human patients and experimental models.[36,37] Similarly, the abundance of *Streptococcus* spp. is significantly higher in elderly patients with prior major illnesses, particularly those affected by stroke.[38] Increased levels of SCFA-producing bacteria, such as *Odoribacter*, *Akkermansia*, Ruminococcaceae, and *Victivallis*, have also been observed. Importantly, stroke severity and functional outcomes have been shown to correlate positively with the abundance of Christensenellaceae and Ruminococcaceae, and negatively with *Enterobacter*, suggesting a complex relationship between microbial profiles and stroke prognosis.[37] Moreover, alterations in the levels of beneficial bacteria (eg, *Lactobacillus*) have been observed in

the gut microbiota of stroke patients, with further analyses identifying specific bacterial genera as independently associated with IS.[39,40] Although *Bifidobacterium* is typically regarded as a beneficial genus, studies have reported contrasting findings regarding its levels in stroke patients—some showing increased abundance, while others reporting a decrease.[41-43] Its early overexpression may indicate a dysregulated response, suggesting a potential role in stroke progression and prognosis. Furthermore, alterations in the gut microbiota have also been observed in several conditions known to elevate the stroke risk. These include increased *Lactobacillus* and decreased *Roseburia* abundance in atherosclerosis; a higher Firmicutes / Bacteroides ratio in hypertension; elevated *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcus viridans* abundance in heart failure; increased Firmicutes and decreased Bacteroides presence in obesity and type 2 diabetes; and elevated levels of Firmicutes, Proteobacteria, and Actinobacteria in chronic kidney disease. These findings underscore the broader role of gut dysbiosis in the pathogenesis of stroke and its associated risk factors.[44-46] Despite some variability, these microbial shifts suggest that IS induces a consistent and reproducible pattern of gut dysbiosis, characterized by a reduction in health-promoting taxa and an expansion of opportunistic species.

Microbial metabolites and stroke Gut microbial metabolites are integral to communication between the gut and the brain, and several of them have been implicated in stroke pathophysiology. Elevated levels of TMAO have been associated with increased atherogenesis, endothelial dysfunction, and platelet aggregation.[47,48] Elevated TMAO levels in plasma are associated with stroke risk factors, and have also been linked to a higher risk of stroke recurrence, particularly in patients with a small artery occlusion subtype.[49] Several studies have shown that high TMAO levels correlate with infarct size and worse outcomes; therefore, elevated levels of TMAO could serve as a prognostic factor of unfavorable outcomes in IS patients.[50]

In contrast, SCFAs exert a wide range of beneficial effects. They support the integrity of the gut epithelial barrier, suppress proinflammatory cytokines, and modulate immune cell differentiation.[51,52] Butyrate, in particular, crosses the BBB and exerts neuroprotective effects by inhibiting histone deacetylases, thereby promoting anti-inflammatory gene expression and enhancing neurotrophic signaling. Treatment with sodium butyrate significantly reduced infarct size and neurological deficits in rats, and attenuated inflammation by decreasing levels of proinflammatory cytokine, such as interleukin (IL)-1β and IL-18. These effects were associated with enhanced histone acetylation, suggesting that epigenetic modulation plays a key role in the observed neuroprotection.[53]

Other important microbial products include bile acid derivatives. Dysregulation of bile acid metabolism, particularly the balance between primary and secondary bile acids, can impact vascular tone, lipid metabolism, and immune responses.[54,55] Secondary bile acids interact with receptors such as FXR and TGR5 to modulate inflammation and endothelial function.[56] Activation of these receptors by bile acids can influence central nervous system functions and may have implications for stroke outcomes. Higher serum total bile acid levels in patients with acute IS or transient ischemic attack are associated with better functional outcomes and a lower risk of severe disability, an effect likely mediated by bile acid receptor activation—particularly TGR5—which modulates neuroinflammation and supports neurological recovery.[57]

Immune-mediated gut–brain interactions in ischemic stroke The immune system serves as a key mediator in the gut–brain dialogue, both during and after IS. Immediately following stroke, the immune system is rapidly activated in response to brain injury, leading to the release of immunologically active molecules known as damage-associated molecular patterns (DAMPs). This initiates an inflammatory cascade, promoting systemic cytokine release and gut immune activation.[58] DAMPs, such as high mobility group box 1, activate pattern recognition receptors on innate immune cells, including monocytes and macrophages, leading to the production of proinflammatory cytokines, such as tumor necrosis factor α and IL-6.[59] Coupled with ischemia-induced autonomic dysfunction and reduced intestinal perfusion, these events foster an environment of increased gut permeability (or "leaky gut"), allowing microbial antigens and toxins to translocate into the systemic circulation. This leakage may exacerbate the stroke-induced inflammatory response and impair tissue repair mechanisms.[60,61]

TLRs, particularly TLR4, are pivotal in this cascade. Activated by bacterial LPS translocated from the gut, TLR4 signaling in microglia and astrocytes promotes cytokine release, matrix metalloproteinase (MMP) activation, and BBB breakdown.[62,63] These changes not only worsen cerebral edema and increase infarct size but also contribute to long-term neurological deficits.[64] LPS/TLR4 activation also impacts the enteric nervous system, altering neuronal survival and impairing gastrointestinal function.[65]

Adaptive immunity is also significantly influenced by gut–brain interactions in IS. $CD4^+$ T-cell subsets, especially proinflammatory type 1 T-helper (Th1) and Th17 cells, play critical roles in augmenting neural damage.[66] In contrast, regulatory T cells (Tregs), particularly $CD4^+CD25^+Foxp3^+$ cells, secrete anti-inflammatory cytokines, such as IL-10 and transforming growth factor β, to mitigate neuroinflammation.[67] IS often leads to a reduction in circulating and tissue-resident Treg

levels, tipping the balance in favor of proinflammatory responses. Experimental models show that restoring Treg populations improves functional outcomes, reduces infarct volume, and limits secondary neuroinflammatory damage.[68]

Gut microbiota and ischemic stroke etiologies In patients with atrial fibrillation (AF), significant gut microbiota alterations have been reported, including increased abundance of *Ruminococcus*, *Streptococcus*, *Enterococcus*, *Parabacteroides*, and *Lachnoclostridium*, along with decreased abundance of *Faecalibacterium*, *Oscillibacter*, *Alistipes*, and *Bilophila*.[69] The duration of AF also influences microbial composition, with progressive reductions in *Butyricicoccus* and *Paraprevotella*, alongside increases in *Blautia*, *Dorea*, and *Coprococcus*, suggesting that sustained dysbiosis parallels AF progression.[70] Elevated TMAO levels in AF correlate with enhanced platelet activation and a higher stroke risk, reflecting the role of microbial metabolites in cardioembolism.[71]

In atherosclerotic IS, dysbiosis is characterized by a reduction in Bacteroidetes and enrichment of Firmicutes, Enterobacteriaceae, oral-origin bacteria, and Clostridia, with specific increases in *Escherichia coli*, *Klebsiella pneumoniae*, and *Bacteroides eggerthii*. These microbial shifts are closely associated with elevated levels of TMAO and systemic inflammatory cytokines, as well as endothelial dysfunction, all contributing to atherothrombotic risk.[72]

Cryptogenic stroke (CS), in which no clear etiology is identified, also demonstrates characteristic microbiota alterations. Patients exhibit increased abundance of Enterobacteriaceae, Streptococcaceae, and Lactobacillaceae, and, at the genus level, *Klebsiella*, *Escherichia–Shigella*, *Streptococcus*, and *Lactobacillus*, which correlates with higher National Institutes of Health Stroke Scale scores, larger infarct volumes, and systemic inflammatory activation. Elevated C-reactive protein, LPS, and LPS-binding protein levels and leukocyte counts in CS suggest increased intestinal permeability and endotoxemia, linking dysbiosis to both infarct severity and worse outcomes.[73]

These findings indicate that microbial characteristics vary by stroke etiology. AF-related stroke is primarily associated with dysbiosis affecting cardioembolism and metabolic mediation. Atherosclerotic stroke reflects chronic dysbiosis with proatherogenic metabolite production. CS exhibits inflammation-driven dysbiosis linked to systemic endotoxemia and infarct severity. Future research that separates stroke by its cause could help identify specific microbial markers and lead to more personalized prevention or treatment approaches.

Comparative insights: gut microbiota in ischemic stroke vs myocardial infarction While IS is associated with reduced microbial diversity, it also involves characteristic compositional shifts, including overgrowth of Enterobacteriaceae (eg, *Escherichia coli*) and *Streptococcus* spp., along with variable changes in beneficial taxa, such as *Lactobacillus*, *Bifidobacterium*, and SCFA-producing bacteria (eg, *Odoribacter*, *Akkermansia*, and Ruminococcaceae).[36,37,41-43] Acute myocardial infarction (AMI) also exhibits shifts in gut microbiota, characterized by increased abundance of *Megasphaera*, *Butyricimonas*, *Acidaminococcus*, *Desulfovibrio*, and *Bifidobacterium*, alongside a reduction in beneficial genera, such as *Faecalibacterium*, *Roseburia*, *Dialister*, and *Prevotella*.[74] Both IS and AMI are associated with elevated circulating levels of TMAO, a gut microbiota–derived metabolite known to enhance platelet reactivity and promote atherothrombosis. In AMI, higher plasma TMAO levels have been linked to an increased risk of major adverse cardiovascular events, all-cause mortality, and recurrent MI, highlighting its prognostic relevance in the postinfarction setting.[50,75]

In IS, stroke-induced autonomic dysfunction and intestinal hypoperfusion trigger acute gut barrier breakdown, allowing systemic translocation of LPS, which activates TLR4-mediated neuroinflammation and contributes to BBB disruption. Elevated plasma LPS levels have been detected early after stroke, correlating with greater infarct progression and secondary brain injury in both human and experimental studies.[62,63] In contrast, AMI seems to be associated with low-grade endotoxemia, which appears to arise primarily from chronic metabolic dysregulation rather than acute intestinal barrier failure.[76] This persistent endotoxemia contributes to vascular inflammation, endothelial dysfunction, and thrombosis through multiple mechanisms, including TLR4-mediated platelet activation, endothelial secretion of procoagulant factors (eg, von Willebrand factor and factor VIII), and increased oxidative stress impairing nitric oxide bioavailability. Furthermore, LPS has been detected within coronary thrombi and atherosclerotic plaques, implicating it not only as a biomarker but also a potential trigger of both acute and chronic cardiovascular events.[77]

Overall, both IS and AMI share a TMAO-driven prothrombotic pathway, but only IS exhibits acute, LPS-mediated gut–brain feedback loops, whereas AMI reflects chronic low-grade endotoxemia influencing systemic vascular and clot biology.

Gut microbiota and ischemic stroke complications

Hemorrhagic transformation Hemorrhagic transformation (HT) is a common complication of IS, independent of reperfusion therapy, that can worsen patient outcomes.[78] Gut microbiota alterations, peripheral inflammation, and SCFAs can modulate MMP-9 levels and weaken the BBB, increasing the HT risk. HT was found to be associated with higher levels of anaerobic bacteria, such as Actinobacteria, Proteobacteria, and Verrucomicrobia.[79] Another clinical and experimental study showed that HT patients had

TABLE 1 Gut microbiota alterations in poststroke complications

Poststroke complication	Observed microbiota changes	Observed molecular changes
HT	*Escherichia*↑, *Shigella*↑, *Actinobacteria*↑, *Proteobacteria*↑, *Verrucomicrobia*↑	LPS↑, LBP↑, sCD14↑, zonulin↓, MMP9↓
PSCI	*Streptococcus*↑, *Klebsiella*↑, *Lactobacillus*↑, *Prevotella*↑, *Veillonella*↑, Bacteroides↑, *Clostridium* XIVa↑, *Parabacteroides*↑, *Roseburia*↓, *Fusicatenibacter*↓, Clostridiaceae↑, Proteobacteria↑, Bacteroidaceae↑, Lachnospiraceae↑, Veillonellaceae↑	IL-6↑, IL-1β↑, SCFA↓
PSD	*Enterococcus*↑, *Escherichia coli*↑, *Bifidobacterium*↓	IL-1↑, IL-2↑, IL-6↑, hs-CRP↑
PSCCID	Trichospiridae↓	SCFA↓
PSE	*Escherichia*↑, *Shigella*↑, *Clostridium innocuum*↑, *Faecalibacterium*↓, *Butyricicoccus*↓	tryptophan↓, fatty acids↓

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; HT, hemorrhagic transformation; IL, interleukin; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; MMP9, matrix-metalloproteinase 9; PSCCID, poststroke cognitive and communicative impairment with depression; PSCI, poststroke cognitive impairment; PSD, poststroke depression; PSE, poststroke epilepsy; SCFA, short-chain fatty acid; others, see **FIGURE 1**

distinct gut profiles, as compared with non-HT and healthy controls, with increased abundance of *Escherichia–Shigella* and *Escherichia coli*.[80] These patients also had elevated plasma levels of LPS, LPS-binding protein, and sCD14, indicating activation of LPS-induced inflammatory pathways. These findings highlight the gut–brain axis as a potential therapeutic target for HT prevention.

Poststroke cognitive impairment and depression Poststroke cognitive impairment (PSCI) is a frequent neuropsychiatric complication of IS. A meta-analysis of 12 Chinese studies showed elevated levels of Proteobacteria, Bacteroidaceae, Lachnospiraceae, and Veillonellaceae families in PSCI, and greater abundance of *Bacteroides*, *Clostridium* XIVa, and *Parabacteroides* at the genus level. Jeng et al[81] reported that PSCI patients had greater abundance of Bacteroidaceae and Clostridiaceae, while non-PSCI individuals had more Prevotellaceae, Ruminococcaceae, Oscillibacter, and Faecalibacterium. Importantly, the Ruminococcaceae family remained significantly associated with cognitive outcomes even after adjusting for confounding variables.

Poststroke depression (PSD) is another serious neuropsychiatric issue following IS. PSD has been increasingly linked to alterations in the gut microbiota, reflecting the broader role of the gut–brain axis in neuroinflammation and mood regulation. A meta-analysis of 9 studies showed that PSD patients had more Proteobacteria, Bacteroidetes, and Fusobacteria, and fewer Firmicutes. This shift reflects a proinflammatory gut environment. Gram-negative bacteria producing LPS may further enhance immune activation and BBB disruption, contributing to depression.[82] Another meta-analysis, incorporating 14 studies, found that PSD patients had significantly higher α-diversity indices (Chao1, Abundance-based Coverage Estimator, Shannon, and Simpson), as compared with healthy controls. Additionally, the relative abundance of Bacteroidota, Fusobacteriota, and Pseudomonadota was higher in the PSD patients, while Bacillota was more abundant in healthy controls.[83] Both PSCI and PSD show distinct microbiota changes that affect neuroinflammation and recovery.

Poststroke epilepsy Gut microbiota may also contribute to poststroke epilepsy (PSE). A recent study compared healthy individuals, stroke patients, and individuals with PSE. Both stroke and PSE patients had reduced microbial diversity. *Escherichia–Shigella* and *Clostridium innocuum* levels were higher in the patients with PSE, while *Faecalibacterium* and *Butyricicoccus* were less abundant in this group. Metabolic pathway analysis showed reduced tryptophan and fatty acid biosynthesis. These findings suggest distinct gut microbial patterns may promote PSE and could serve as diagnostic or therapeutic targets.[84]

The microbial and molecular changes in poststroke complications are summarized in **TABLE 1**.

Therapeutic strategies

Diet Diet profoundly influences the MGBA, impacting the IS risk and outcomes. Western diets, characterized by high salt, fat, and sugar content, as well as alcohol consumption, disrupt the gut microbiota balance, leading to increased inflammation and a higher risk of stroke.[85] These diets, along with low fiber intake, can raise the CVD and stroke risk by promoting hypertension, metabolic disorders, atherosclerosis, and vascular dysfunction.[86] In contrast, high intake of dietary fiber and polyunsaturated fatty acids (PUFAs), especially omega-3 PUFAs, promotes beneficial gut microbiota (eg, *Bifidobacterium*) while inhibiting Enterobacteriaceae, reduces systemic inflammation, and is protective against stroke.[87] Dietary fiber may lower the stroke risk by reducing blood pressure, lipid levels, and inflammation, supporting beneficial gut microbiota colonization and diversity and SCFA production, lowering TMAO levels, and improving bowel function. Omega-3 and omega-6 fatty acids support stroke prevention and recovery by regulating lipid levels, reducing inflammation, protecting vessels and neurons, and improving cognitive and motor function. A balanced intake, especially from sources such as fish, flaxseeds, and walnuts, is very important.[88] Mediterranean diet, characterized by consumption of plant-based foods and healthy fats as well as moderate fish intake, has shown protective effects against stroke, and supports recovery by reducing inflammation, improving vascular health, and stabilizing lipid and glucose levels through improved metabolic and microbial profiles.[89] Intermittent fasting has been shown to enhance gut microbiota diversity and increase the abundance of beneficial bacterial families,

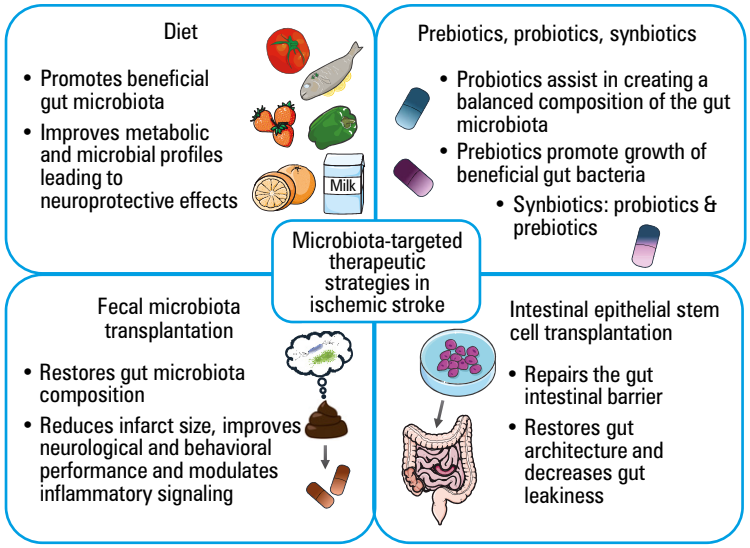

FIGURE 2 Microbiota-targeted therapeutic strategies in ischemic stroke. The Figure summarizes treatments that influence the gut-brain axis and may improve stroke outcomes. Dietary approaches support beneficial gut bacteria and reduce inflammation. Probiotics, prebiotics, and synbiotics enhance microbial balance and modulate immune signaling, contributing to neuroprotection. Fecal microbiota transplantation introduces healthy microbes and reduces stroke-related tissue damage. Transplantation of intestinal stem cells can repair the gut barrier and lower inflammation that affects the brain.

such as Lactobacillaceae, Bacteroidaceae, and Prevotellaceae. These microbial shifts are associated with the activation of antioxidant metabolic pathways, exerting neuroprotective effects.[90] Thus, diet-driven modulation of the gut–brain axis offers a promising avenue for IS prevention and therapeutic intervention.

Prebiotics, probiotics, and synbiotics Probiotics are microorganisms that colonize the small intestine, offering beneficial effects to the host. Administration of probiotics helps create a balance between commensal and pathogenic gut bacteria through lactic acid fermentation.[91] Probiotics, such as *Bifidobacterium*, *Lactobacillus*, and *Clostridium butyricum*, have been shown to reduce stroke severity and improve outcomes.[92] *Bifidobacterium* contributes to maintaining a healthy gut microbiota by suppressing harmful bacteria, reinforcing the intestinal barrier, and limiting translocation of toxic substances into the bloodstream. This helps lower systemic inflammation and protects the nervous system. Similarly, *Lactobacillus* supports gut health by adhering to the intestinal lining, reducing the levels of pathogenic bacteria, and strengthening mucosal integrity. It also regulates immune activity, mitigates neuroinflammation through the MGBA, and promotes neural recovery, highlighting its neuroprotective potential.[88] Probiotics can help lower blood pressure—a key stroke risk factor—by reshaping the gut microbiota and modulating inflammatory and neuroimmune responses. Their beneficial effects include reducing the levels of proinflammatory cytokines (eg, tumor necrosis factor α), limiting oxidative stress via gut epithelial TLR signaling, lowering TMAO levels, enhancing brain-derived neurotrophic factor production, preventing cell death, and increasing beneficial gut bacteria. These actions highlight the therapeutic potential of probiotics in managing hypertension and stroke.[85,93] Prebiotics, such as inulin and oligosaccharides, are nondigestible compounds with no biological activity that promote growth and reproduction of beneficial gut bacteria, thus enhancing therapeutic effects of probiotics.[91] Supplementation of inulin and fructooligosaccharides has been shown to promote *Bifidobacterium* growth. β-Glucan, another prebiotic, may help lower low-density lipoprotein and total cholesterol levels, stabilize blood glucose, and improve endothelial function (likely through SCFA production), contributing to cardiovascular protection.[3] Lactulose is an important prebiotic that increases SCFA levels in the intestine and bloodstream, reduces inflammation following stroke, and enhances poststroke functional recovery.[94] Synbiotics, a combination of probiotics and prebiotics, exhibit synergistic benefits, demonstrated through improved neurological and cognitive functions in animal stroke models, reduction of infarct size, and attenuation of inflammatory pathways.[91,95] In summary, probiotics and prebiotics may support stroke prevention and recovery. Their consumption or supplementation can be a helpful adjunct to conventional treatment.

Fecal microbiota transplantation Fecal microbiota transplantation (FMT) is the most effective method for restoring the gut microbiota composition, and shows promise as a therapeutic strategy for IS. It can improve stroke outcomes by alleviating gastrointestinal symptoms and enhancing immune function, and has the potential to reduce neuroinflammation after stroke. FMT may be protective against ischemic damage by lowering IL-17, interferon-γ, and proapoptotic Bax levels, while increasing antiapoptotic Bcl-2 expression.[96,97] Furthermore, it reduces cerebral ischemic injury and improves neurological deficits, likely by decreasing oxidative stress, apoptosis, and inflammation, and can positively influence several stroke-related parameters, including reducing infarct size, improving neurological and behavioral performance, and enhancing survival.[98,99]

Intestinal epithelial stem cell transplant Intestinal epithelial stem cell transplantation has emerged as a promising therapeutic approach for stroke recovery, particularly through its impact on the gut–brain axis. This method has been shown to restore gut architecture and decrease gut leakiness, thereby reducing circulating levels of LPS and inflammatory cytokines, such as IL-17A. By repairing the gut barrier, intestinal epithelial stem cells help prevent the translocation of proinflammatory molecules into the bloodstream, stopping them from reaching the brain and exacerbating neuroinflammation.[100]

Therapeutic strategies targeting the gut microbiota that modulate the gut–brain axis and potentially improve stroke outcomes are summarized in FIGURE 2.

Conclusions The interplay between the gut microbiota and IS has emerged as a significant area of research, revealing a complex and bidirectional relationship mediated through the gut–brain axis. Dysbiosis, characterized by reduced microbial diversity and disrupted metabolite production, contributes to IS pathogenesis by promoting systemic inflammation, endothelial dysfunction, and neurovascular injury. Microbial metabolites, such as TMAO, SCFAs, and bile acid derivatives, have been implicated in key pathogenic processes, including atherosclerosis, immune modulation, and disruption of BBB integrity. The immune system is a key mediator of gut–brain interactions during and after IS. Brain injury triggers the release of DAMPs (eg, high mobility group box 1), which activate inflammatory pathways and increase gut permeability. This allows microbial products, such as LPS, to enter circulation and activate TLR4, worsening neuroinflammation and BBB disruption. Meanwhile, a shift toward proinflammatory Th1/Th17 cells and reduced Tregs further impairs recovery. Alterations in gut microbiota composition also influence poststroke complications, such as HT, cognitive impairment, depression, and epilepsy. Therapeutic strategies targeting the gut microbiota, including dietary modification, probiotics, prebiotics, and synbiotics, FMT, and intestinal epithelial stem cell therapy, show promise to mitigate IS severity and improve recovery outcomes. While many findings stem from preclinical studies, emerging clinical data support the relevance of microbiota-focused interventions. Continued research is essential to identify specific microbial signatures and validate microbiome-based therapies as adjuncts to conventional stroke management. Ultimately, targeting the gut microbiota offers a novel and integrative approach to preventing IS, reducing its complications, and enhancing long-term neurological recovery.

ARTICLE INFORMATION

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