Gut microbiota and stroke: New avenues to improve prevention and outcome

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REVIEW ARTICLE

Gut microbiota and stroke: New avenues to improve prevention and outcome

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Abstract

Despite major recent therapeutic advances, stroke remains a leading cause of disability and death. Consequently, new therapeutic targets need to be found to improve stroke outcome. The deleterious role of gut microbiota alteration (often mentioned as "dysbiosis") on cardiovascular diseases, including stroke and its risk factors, has been increasingly recognized. Gut microbiota metabolites, such as trimethylamine-*N*-oxide, short chain fatty acids and tryptophan, play a key role. Evidence of a link between alteration of the gut microbiota and cardiovascular risk factors exists, with a possible causality link supported by several preclinical studies. Gut microbiota alteration also seems to be implicated at the acute phase of stroke, with observational studies showing more non-neurological complications, higher infarct size and worse clinical outcome in stroke patients with altered microbiota. Microbiota targeted strategies have been developed, including prebiotics/probiotics, fecal microbiota transplantation, short chain fatty acid and trimethylamine-*N*-oxide inhibitors. Research teams have been using different time windows and end-points for their studies, with various results. Considering the available evidence, it is believed that studies focusing on microbiota-targeted strategies in association with conventional stroke care should be conducted. Such strategies should be considered according to three therapeutic time windows: first, at the pre-stroke (primary prevention) or post-stroke (secondary prevention) phases, to enhance the control of cardiovascular risk factors; secondly, at the acute phase of stroke, to limit the infarct size and the systemic complications and enhance the overall clinical outcome; thirdly, at the subacute phase of stroke, to prevent stroke recurrence and promote neurological recovery.

KEYWORDS
cardiovascular risk factor, microbiota, stroke, SCFA, TMAO

INTRODUCTION

Stroke is the second most common cause of death and a leading cause of disability worldwide. Current treatments aim to restore brain perfusion as soon as possible to preserve the ischaemic penumbra, that is, the severely hypoperfused, electrically silent, at-risk brain tissue. Reperfusion therapies, such as recombinant tissue plasminogen activator and mechanical thrombectomy for selected patients with large vessel occlusion, have demonstrated their efficacy in improving clinical outcome. However, over 50% of patients

have a poor functional outcome despite timely and effective reperfusion. Moreover, a large proportion of patients cannot access those treatments within an appropriate time window. Therefore, there is a need to develop novel strategies to improve both stroke prevention and the efficiency of reperfusion therapies.

Gut microbiota has been a subject of growing interest over the last decade. The gut microbiota is a community of micro-organisms, including bacteria, viruses, fungi and archaea, that inhabit mostly the large intestine and consist of tens of trillions of microorganisms [1]. It is shaped by host genes, age, diet, xenobiotics such as antibiotics, and digestive and extra-digestive diseases. It plays many roles, from local barrier against pathogens to maturation of the immune system and secretion of metabolites [1]. The latter can be derived from microbial metabolism of dietary substrates, such as short chain fatty acids (SCFAs), trimethylamine-*N*-oxide (TMAO) and tryptophan metabolites. SCFAs, mainly acetate, propionate and butyrate, are produced by commensal microbiota through fermentation of indigestible non-starch polysaccharides (dietary fibers). TMAO comes from the degradation of choline, carnitine and phosphatidylcholine, present in food, by specific intestinal bacteria. Tryptophan is an essential amino acid whose metabolism is tightly controlled in the gut where it can be processed by bacteria to indole derivatives with various physiological functions [2]. Metabolites may also come from modification of host molecules, such as bile acids (BAs), or directly from bacteria.

Several studies support a bidirectional interconnection between the gut microbiota and the brain through the gut–brain axis [3]. Top-down signaling (from the brain to the gut) involves parasympathetic and sympathetic fibers directly connected to the gut wall, but also to the enteric nervous system. The hypothalamic–pituitary–adrenal axis is also involved. This descending system has an impact on gut motility, gut permeability, microbiota makeup and resident immune cell activation [3]. Bottom-up signaling (from the gut to the brain) occurs through activation of the vagus nerve by bacterial compounds, metabolites and hormones, but also through the direct effect of metabolites, such as neurotransmitters (noradrenaline, dopamine, serotonin) and immunogenic endotoxins (such as lipopolysaccharides) [3] that enter the bloodstream and cross the blood–brain barrier.

Increasing evidence, including both preclinical and clinical studies, has shown that alteration of the gut microbiota (often mentioned as "dysbiosis", characterized as a disruption of the microbiota normal homeostasis) might play a key role in numerous neurological diseases, including stroke [4]. The effect is mediated by the gut–brain axis and is mainly explained by a modeling of the immune system towards the proinflammatory side and a switch in secretion of metabolites toward noxious ones [4–6]. SCFA, TMAO and tryptophan metabolites as well as BA metabolism are particularly involved in this process [7] (Figure 1).

Here, first data on the impact of gut microbiota alteration on stroke risk and outcome are summarized and discussed, before the gut-microbiota-targeted strategies that could be applied in patients to improve stroke prevention and outcome are considered.

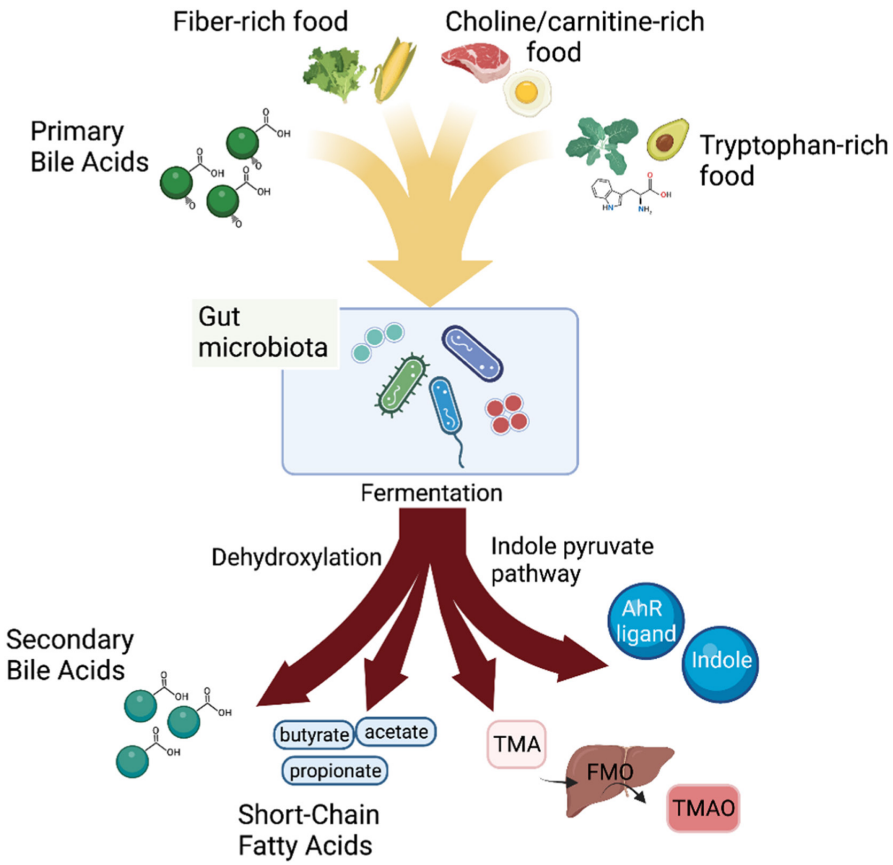

FIGURE 1 Gut microbiota metabolites involved in stroke. From food and primary bile acids, the gut microbiota produce (i) secondary bile acids by partial dehydroxylation of primary bile acids; (ii) short chain fatty acids by fermentation of fiber-rich food; (iii) trimethylamine (TMA) through fermentation of choline/carnitine-rich food and (iv) indole derivatives with aryl hydrocarbon receptor (AhR) ligands. TMA will in turn be metabolized to trimethylamine-*N*-oxide (TMAO) by flavin monooxygenase (FMO) in the liver. Created with BioRender.com.

IMPACT OF GUT MICROBIOTA ALTERATION ON STROKE RISK AND OUTCOME

Gut microbiota alteration and stroke risk factors

There are currently few data available on the relationship between gut microbiota alteration and the risk of stroke. Some cohort studies have inconsistently reported an association between high TMAO levels and incident stroke in high risk patients [8].

In contrast, there is increasing evidence that the composition and metabolism of the gut microbiota are associated with known stroke risk factors, with some studies even suggesting causality. Interestingly, common deleterious metabolic pathways and molecular intermediates may be involved in several risk factors. In particular, decreased SCFA production, increased TMAO production and imbalance in indole derivative production by the gut microbiota are associated with a higher blood pressure, metabolic syndrome, atherosclerosis and low-grade vascular inflammation.

Hypertension

Several animal and human studies have shown that modification of the gut microbiota is present in hypertensive individuals and may support the link between diet and hypertension.

In humans, several cross-sectional studies have consistently shown a reduced gut microbiota diversity as well as a high abundance of Gram-negative bacteria and low abundance of SCFA-producing bacteria in hypertensive patients compared to normotensive subjects [9–11]. In animal models of hypertension, there is also a decrease in microbial richness associated with a decrease in acetate- and butyrate-producing bacteria and an increase in lactate-producing bacteria compared with normotensive counterparts [9].

Experimental studies also support a causal relationship between gut microbiota composition and blood pressure values [12]. Indeed, germ-free mice receiving fecal microbiota transplantation (FMT) from a spontaneously hypertensive stroke-prone rat or hypertensive human donor developed higher blood pressure than germ-free mice receiving FMT from normotensive donors [13, 14].

Gut microbial metabolites are also associated with blood pressure. Indeed, circulating TMAO levels were associated with blood pressure in humans whilst dietary supplementation with TMAO increased blood pressure and aortic stiffness in mice [15]. Several tryptophan-derived metabolites have also been linked to hypertension via different mechanisms, such as the production of indole that can increase blood pressure when administered via intravenous injection in a rat model [16, 17].

Diabetes

Numerous studies suggest that patients with type 2 diabetes (T2D) have altered gut microbiota compared to healthy individuals.

The results of two large-scale metagenome analyses in China and Europe showed a decrease in abundance of bacteria that produce the SCFA butyrate in the gut microbiota of individuals with T2D [18, 19]. Despite geographical and diet differences, both studies found an increase of *Clostridium hathewayi* and a decrease of *Roseburia* in T2D patients.

Moreover, SCFAs, TMAO and tryptophan-derived metabolites have been reported to be closely associated with T2D. Circulating TMAO levels were associated with insulin resistance in a large human prospective cohort and with T2D [20, 21]. In an opposite way, SCFA supplementation was associated with an increase of glucagon-like peptide-1 (GLP-1) production that favors insulin secretion and glucose metabolism whereas bacterial indole has been shown to inhibit GLP-1 production after long-term exposure [22, 23]. In addition, BA metabolism by the gut microbiota positively regulates synthesis and secretion of insulin and GLP-1 [24].

Dyslipidemia

Few studies have focused on the link between gut microbiota alteration and dyslipidemia.

In a cohort study of 2309 European participants, significant associations were found between some bacteria families and serum high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels [25]. Moreover, fecal transplant from patients with altered cholesterol levels was able to transfer this abnormality to germ-free mice, supporting a causal role of dysbiosis in dyslipidemia [26].

The role of gut-microbiota-derived metabolites on dyslipidemia and lipid metabolism is being increasingly studied [27]. SCFA supplementation in rodents has been shown to reduce total cholesterol and triglycerides [28]. Data regarding TMAO are more conflicting, with some studies showing that TMAO consumption reduced cholesterol intestinal absorption and others that TMAO supplementation increased circulating lipid levels [27]. The deleterious effect of TMAO on lipid metabolism seems to be mediated by an increase in cholesterol deposition in peripheral tissues rather than by a direct effect on circulating lipid levels [5, 27]. Finally, BA cascade involving bacterial metabolism has a positive effect on lipid and lipoprotein metabolism [24, 27].

Obesity

Obese people, as obese mice, have a marked increase in the *Firmicutes* to *Bacteroidetes* ratio whereas weight loss due to dietary restriction of fat and carbohydrates is associated with a relatively higher abundance of *Bacteroidetes* [29]. Experimental studies support a causal relationship between gut microbiota composition and obesity. Germ-free mice receiving FMT from conventionally raised mice have a dramatic increase in body fat [30]. Importantly, another study has observed a higher increase

in body fat in germ-free mice colonized by microbiota harvested from obese donors than in those colonized by microbiota harvested from lean donors [31].

A recent meta-analysis revealed a positive dose-dependent association between circulating TMAO levels and obesity in humans [32].

Vascular inflammation and thrombosis

Several studies have shown that gut microbiota composition from patients with atherosclerosis differed from control subjects [33]. Different bacteria were also present in the plaque [33].

Besides, circulating levels of TMAO have been shown to be associated with imaging features of vulnerable plaques and the risk of clinical events in coronary artery disease patients [34, 35]. Moreover, TMAO has been shown to favor platelet activation and thrombosis after arterial injury and induce proinflammatory change in arterial walls [36–38]. In addition, altered tryptophan metabolism by the gut microbiota with indoxyl sulfate production induces pro-atherogenic inflammation on the vascular endothelium [16].

Atrial fibrillation

Emerging evidence suggests a link between microbiota and atrial fibrillation (AF) beyond concomitant comorbidities.

Gut microbiota richness and diversity seem to differ in patients with AF but results are conflicting [39]. A recent experimental study showed that high AF susceptibility of aged rats could be transmitted to young rats using FMT and was associated with higher circulating lipopolysaccharide levels and atrial NOD-like receptor protein 3 (NLRP3) inflammasome activity. In an opposite way, applying FMT in aged rats with youthful microbiota suppressed the development of age-related AF [39, 40].

In addition, some studies demonstrated that circulating TMAO levels were associated with the incidence and the progression of AF, possibly by regulating cardiac autonomic nerves [41, 42].

Gut microbiota alteration and stroke severity and outcome

A growing number of studies highlight the strong relationship between alteration of the composition and function of gut microbiota and stroke severity, non-neurological complications and post-stroke disability (Figure 2). As presented in the introduction, the microbiota–gut–brain axis is a two-way communication. Therefore, it is not surprising that numerous studies have shown that stroke induces alterations of the gut microbiota [3].

Some authors have tried to map the gut microbiota in post-stroke human patients using case–control studies, with various and sometimes conflicting results. The results of these studies have been summarized by Peh et al., but their pooling is hampered by the fact that the methodology (stool collection and storage) and population (probiotic and antibiotic use before inclusion) are often heterogeneous or with missing data [4]. A higher prevalence of the phyla *Actinobacteria*, *Proteobacteria*; class *Gammaproteobacteria*; families *Bacteroidaceae*, *Bifidobacteriaceae*, *Enterobacteriaceae*, *Lachnospiraceae*, *Porphyromonadaceae*, *Prevotellaceae*, *Rikenellaceae*, *Ruminococcaceae* and *Veillonellaceae*; genera *Bacteroides*, *Escherichia/Shigella*, *Lactobacillus*, *Prevotella*, *Ruminococcus* and *Streptococcus* was reported in post-stroke patients compared to healthy controls, along with a lower prevalence of phyla *Bacteroidetes* and *Firmicutes*, and genera *Eubacterium*, *Faecalibacterium* and *Roseburia* [4]. Bacterial diversity was also reduced in most studies. Note that most of these studies (13/14) were carried out on Chinese patients and focused on gut bacterial microbiota, with little information on their metabolites. Whether gut microbiota changes were prior to stroke or were triggered by it remains unknown.

However, several animal studies have confirmed the post-stroke gut microbiota changes and have examined further the crosstalk between gut microbiota composition and stroke. In experimental models, large stroke lesions can induce gut microbiota alteration through modification of gut physiology, with reduction of gastrointestinal motility and bacterial overgrowth [3]. In turn, post-stroke changes of the gut microbiota can affect stroke outcome. Indeed, colonizing germ-free mice with an altered gut microbiota from mice or humans who underwent a stroke caused a larger infarct volume and a worse neurological deficit after acute middle cerebral artery occlusion compared to mice with normal microbiota [6, 43]. This deleterious effect seems to be in part linked to a proinflammatory T-cell polarization in the intestinal immune compartment and in the ischaemic brain [6, 43]. Regarding metabolites, a case–control study showed that SCFA levels were lower in acute ischaemic stroke (AIS) patients compared to healthy controls and negatively correlated with stroke severity [44]. Germ-free mice receiving FMT from a human donor with high TMAO levels had increased plasma TMAO levels and a larger infarct volume compared to those receiving FMT from a human donor with low TMAO levels [45]. In the same way, feeding mice with choline or TMAO before stroke or transplanting a functional gut microbial choline utilization C (CutC), a major choline trimethylamine (TMA) lyase that increases TMAO levels, was associated with a larger infarct volume and a worse motor deficit [45].

In another work, FMT with fecal microbiota of aged mice increased mortality and neurological deficit after ischaemic-induced stroke in young mice [46]. Conversely, FMT with fecal microbiota of young mice before stroke improved survival and recovery in old mice [46].

In humans, reduced SCFA levels, especially acetate, were associated with a poor functional outcome at 3 months in a case–control study including 140 AIS patients [44]. Recent evidence also suggests a link between gut microbiota alteration and post-stroke cognitive impairment (PSCI) in patients. A cohort of 65 AIS patients showed that those with PSCI at 3 months had a lower gut microbiota alpha diversity, a 10-fold increase of *fusobacterium* and a significant

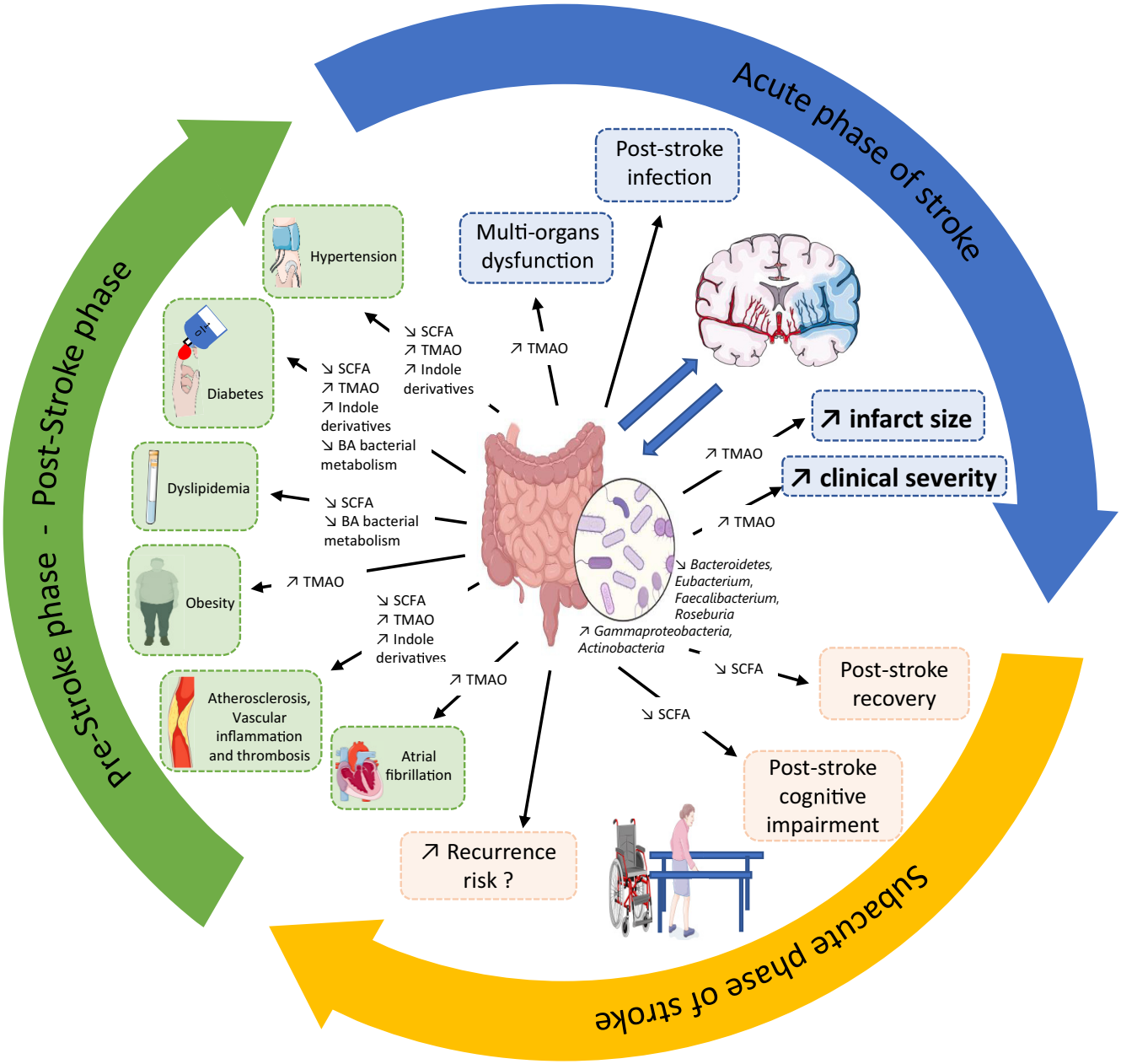

FIGURE 2 Potential impact of gut microbiota alteration on stroke risk and outcome. BA, bile acid; SCFA, short chain fatty acid; TMAO, trimethylamine-*N*-oxide.

decrease in abundance in SCFA-producing germs compared to those without PSCI [47].

Stroke outcome might also be worsened by non-neurological complications occurring in the following days. Post-stroke infection is a well-known complication at the acute phase. Stanley and collaborators [48] assumed that pneumonia in this context might be the consequence of bacterial translocation favored by gut barrier dysfunction following stroke, rather than micro-inhalation. Indeed, they demonstrated that the majority of lung bacteria in individuals developing post-stroke pneumonia were common commensal bacteria that normally reside in the small intestine, and that digestive germ-free mice were unable to develop post-stroke pneumonia [48].

Cardiac complications are reported in approximately 20% of AIS patients. Gut dysbiosis may contribute to this process through bacterial, endotoxin and TMAO translocation to the blood, causing coronary microvascular obstruction, myocardial inflammation and cardiac dysfunction in some patients [49].

GUT-MICROBIOTA-TARGETED STRATEGIES THAT COULD IMPROVE STROKE PREVENTION AND OUTCOME

In this last part the available data on microbiota-targeted strategies in stroke prevention and outcome are reviewed, focusing on clinical

trials and randomized controlled studies. When not available, observational human or even animal studies that reported promising results are presented. Data are summarized in Figure 3.

Stroke prevention

To our best knowledge, few prospective human studies focusing on microbiota have ever used stroke occurrence as a primary endpoint. Therefore, studies detailed below mainly focus on the impact of microbiota-targeted strategies on cardiovascular risk factors, as an indirect way of preventing stroke.

Probiotics and prebiotics

According to the International Scientific Association of Probiotics and Prebiotics, prebiotics are defined as selectively fermented ingredients that result in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefits

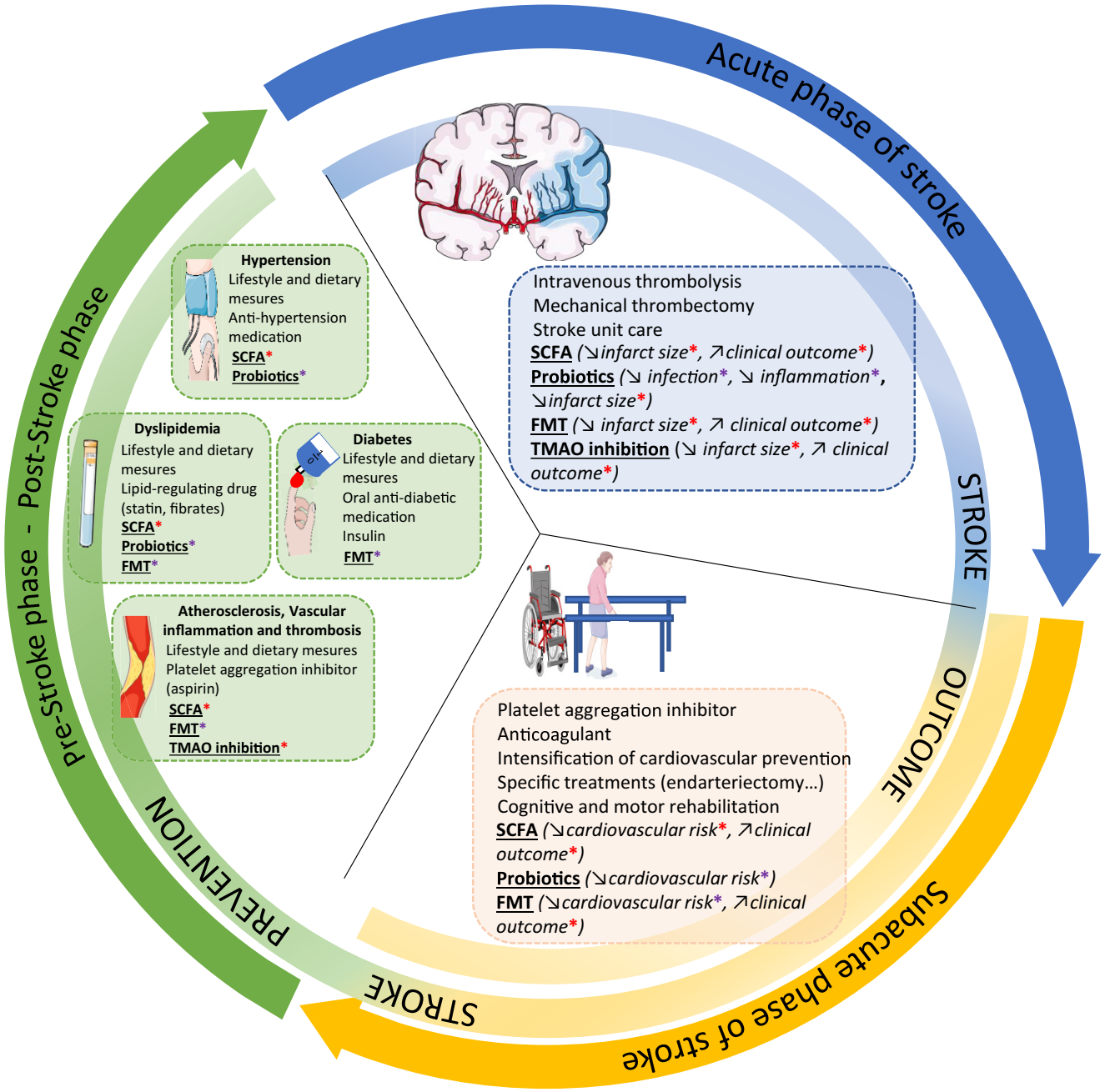

FIGURE 3 Conventional stroke care and the potential place of microbiota-targeted strategies at every phase of stroke. Reference management is indicated in normal characters, and microbiota-targeted strategies are indicated in bold and underlined characters. For each microbiota-related intervention, a purple asterisk indicates that human studies are available, and a red asterisk indicates that only preclinical studies are available. FMT, fecal microbiota transplantation; SCFA, short chain fatty acid.

upon host health [50]. There are many types of prebiotics, most of them being a subset of carbohydrate groups (glucans, glucose-derived oligosaccharides, galacto-oligosaccharides).

A meta-analysis including eight human cohorts concluded that greater total dietary fiber intake was associated with a significantly reduced risk of primary ischaemic or hemorrhagic stroke occurrence [51]. An increase of 7 g of fibers per day regardless of fiber type was associated with a 7% diminution of stroke risk. A phase IIa crossover randomized controlled trial is ongoing to assess whether a diet containing acetylated and butyrylated modified resistant starch can reduce blood pressure levels (Clinical Trial Registry ACTRN12619000916145).

Probiotics are defined by the World Health Organization as live microorganisms which when administered in adequate amounts confer a health benefit on the host. Most common microorganisms are bacteria that belong to the *Lactobacillus* and *Bifidobacterium* groups. Their mechanisms of action include normalization of gut microbiota composition, SCFA production, bacterial BA metabolism, and regulation of intestinal transit between others. In a 2021 review, Wu and Chiou identified a total of four preclinical studies in rodents that investigated the beneficial role of probiotic supplementation before stroke (one of those was a heat stroke model however) [52]. Probiotics have been particularly studied in hypertension, with prospective studies in humans reporting a beneficial effect of both orally administered pure strains (genera *Lactobacillus* and *Bifidobacterium*) and fermented milk products [52]. Similarly, a meta-analysis from 2015 that analyzed 11 randomized control trials concluded that probiotic supplementation could be useful in hypercholesterolemia patients, as a long-term intervention (>4 weeks) with both probiotics and fermented milk was associated with a significant reduction of LDL cholesterol levels without impacting HDL cholesterol levels [53].

Short chain fatty acids/TMAO

Prospective works on the use of SCFAs in humans to reduce cardiovascular risk factors are scarce. One promising animal study published in 2019 using propionate supplementation in two different hypertensive mice models showed a significant diminution of blood pressure levels and aortic atherosclerotic lesion area at 2 weeks and 1 month [54]. This effect was probably T-cell dependent, suggesting again an important role of immune–microbial crosstalk in vascular injuries. Two other preclinical studies have also demonstrated that acetate supplementation, another SCFA, decreased blood pressure but also reduced cardiorenal complications [55, 56]. As discussed before, a previous study also showed a significant diminution of cholesterol level in a rat model of cholesterol-rich diet fed with acetate [28].

Trimethylamine-*N*-oxide production may be modulated without affecting microbial viability by targeting TMA-producing enzyme complexes. In animal models, inhibition of such enzymes using choline utilization C/D (CutC/D) inhibitor significantly reduced plasma TMAO levels and attenuated diet-induced enhanced platelet aggregation and thrombus formation [57].

Fecal microbiota transplantation (FMT)

Fecal microbiota transplantation is defined as the transfer of a fecal preparation from a healthy donor into the gastrointestinal tract of a recipient to induce therapeutic effects.

Currently, it is the most efficient treatment to cure multiple recurrent *Clostridioides difficile* infection by restoring the microbial protective function of the gut microbiota. After bowel cleansing and antibiotic pre-treatment, stool preparations can be administrated through enema, frozen capsule, colonoscopy or gastric/duodenal infusion with mostly only mild and transient gastrointestinal symptoms.

Increasing evidence suggests a potential benefit of FMT on cardiovascular risk factors. Twenty-four patients with a metabolic syndrome transplanted with gut microbiota from healthy donors had a longer thrombinography lag time at 6 weeks compared to control patients, which remains clinically moderately relevant but suggests that correcting dysbiosis in those patients could protect from the associated thrombophilia and risk of cardiovascular event [58]. Two other studies conducted in patients with metabolic syndrome demonstrated that FMT increased patients' insulin sensitivity [59]. In one of these studies, patients with FMT had an increase in butyrate-producing bacteria at 6 weeks compared to controls.

In a recent randomized control study [60] that included 61 obese patients with T2D, combining lifestyle intervention with FMT led to reduced LDL cholesterol levels and liver stiffness at week 24 whilst increasing *Bifidobacterium*, *Lactobacillus* and overall butyrate-producing bacteria [60]. However, in a more recent prospective study including 22 obese patients without T2D who received FMT from a healthy non-obese donor, no change was found in body mass index at 12 weeks despite a significant switch in microbiota composition toward the donor's [61]. However, the duration of the study was probably too short to draw conclusions on such end-point.

Stroke outcome

Probiotics and prebiotics

Two recent meta-analyses have combined case–control and randomized controlled studies that used probiotics at the acute phase of stroke [62, 63]. Those studies compared enteral nutrition and probiotics to enteral nutrition alone, and the main type of probiotics used were *Bifidobacterium* and *Lactobacillus*, with some studies using *Clostridium butyricum*, *Enterococcus faecium*, *Bacillus subtilis* and lactic acid bacteria. Probiotics were associated with a reduced incidence of gastrointestinal complications and systemic infections (pulmonary, digestive and urinary), a shortened hospitalization length and lower levels of some circulating inflammatory markers

(mainly interleukin-6, interleukin-10 and tumor necrosis factor alpha) [62, 63]. However, most of included studies had missing information on randomization and blinding methods and a limited sample size (26 studies including from 56 to 140 patients). No reliable information was reported on stroke prognosis either. Finally, most studies occurred in China, which limits the generalization of the results to Western populations of patients.

Additional data on stroke severity and outcome come from preclinical studies even if the transferability to AIS patients is limited (probiotics given before stroke) [52]. Reduction of infarct volume and improvement of the neurological deficit were observed in rodents, with various probiotics and time frame, such as *C. butyricum* given for 14 days before stroke, a combination of *Lactobacillus* and *Bifidobacterium* given 2 weeks before stroke, or *Lactobacillus* given once 2 h before stroke [52]. Interestingly, all these bacteria are known producers of SCFAs.

Two ongoing clinical trials (https://clinicaltrials.gov/ct2/show/NCT04954846, https://clinicaltrials.gov/ct2/show/NCT03812445) are analyzing the impact of probiotics on stroke outcome, with a focus on cognitive functions.

Short chain fatty acids/TMAO

A rat model of transient middle cerebral artery occlusion showed a smaller infarct size and a better neurological outcome when receiving butyric acid (30 mg/kg) daily for 14 days after stroke [64]. Two other animal studies showed a beneficial impact of SCFAs on post-stroke recovery [65, 66]. In the first one, a 4-week oral supplementation with SCFAs before stroke improved post-stroke recovery by enhancing neuronal plasticity and microglial activity [65]. In the other one, a fecal transplant with SCFA-producing microbiota a few days after stroke improved the recovery irrespective of the infarct volume, with a synergistic effect of bacteria with a prebiotic (inulin) [66]. Despite those interesting results, no work has assessed the effect of SCFA supplementation in AIS patients.

A strategy to reduce TMAO production through transplantation of microbial communities with genetic disruption of CutC (i.e., lack of ability to produce TMA) to germ-free mice prevented TMAO-associated stroke severity, reducing both infarct volume and functional deficit [45].

Fecal microbiota transplantation

No human studies have investigated the impact of FMT at the acute phase of stroke.

Three preclinical studies showed a protective effect of FMT after ischaemic stroke. One study showed that germ-free mice colonized with a healthy gut microbiota had a reduced final infarct volume after middle cerebral artery occlusion [6]. Another showed better functional outcome on motor tests in mice who benefited from FMT a few days after stroke, independently of the infarct size [66]. Finally, in a rat model already mentioned above, FMT performed during 14 days after stroke was associated with a decrease of the final infarct size and the neurological impairment [64]. This effect was probably linked to the upregulation of SCFA production [64].

Further human studies are needed to assess the potential benefit of such an intervention in AIS patients.

CONCLUSION

Increasing evidence suggests a key role of gut microbiota before stroke occurrence (pre-stroke phase) and at every time frame of stroke (acute and subacute phase). This impact is mostly mediated by its metabolites (SCFAs, TMAO, indole derivatives, BAs).

Human studies using microbiota-targeted strategies suggest a positive result on cardiovascular risk factor control. Whilst such human studies are lacking in stroke patients, preclinical studies have obtained promising results using probiotics and prebiotics, SCFAs and FMT. Microbiota-targeted strategies have the added benefit that they are easily accessible and feasible in clinical practice, without major side effects.

These interventions could find a place in stroke patient management, in addition to stroke standard care. However, there is still a significant lack of knowledge to implement these combined strategies in routine stroke care. Two types of clinical research should be prioritized in the coming years to address this gap.

The first would be large-scale prospective observational cohorts aimed at precisely mapping the gut microbiota of stroke patients, along with their serum metabolites, and correlating those findings with relevant data such as stroke severity, stroke subtypes and etiology, lesion volume, occurrence of non-neurological complications and clinical outcome including cognitive function. A solid methodology with regard to stools, serum collection and patient selection (ethnicity, previous medication and diet) should be warranted.

The second would be randomized controlled studies comparing a microbiota-targeted strategy in association with standard care to standard care alone in ischaemic stroke patients, with two time windows of interest. At the acute/subacute phase of stroke, end-points would include clinical outcome, final lesion size, non-neurological complications including infections and cardiac complications. Beyond the acute/subacute phase, end-points would include correction of microbiota alteration, clinical outcome and cardiovascular events including stroke recurrence.

The choice of intervention (prebiotics/probiotics, SCFAs, FMT etc.) should consider the speed and duration of action, the cost and the pharmaceutical form (taking into account the frequent presence of swallowing disorders).

Thus, preliminary data are now sufficient to pave the way for ambitious studies to evaluate the clinical relevance of gut dysbiosis and the potential benefit of microbiota-targeted therapies to improve stroke prevention and outcome.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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