The Gut Microbiota in Cardiovascular Diseases: From Biomarkers and Potential Targets to Personalized Interventions

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\textbf{Abstract: Background:} This study discusses the crucial factors responsible for the progression of atherosclerotic cardiovascular disease (CVD). The interaction between the gut microbiota, heart, and vessels in CVD pathogenesis is extremely complex and includes components such as direct bacterial translocation from the gut to vessels and metabolite-mediated damage. To a greater extent, CVD seems to be entangled with a subtle immune system-to-microbiota interface. From among the most significant advances in recent years in this area, it is necessary to highlight the discovery of the pro-atherogenic effect of trimethylamine-N-oxide (TMAO) and changes in the activity of effector T-cells in the settings of dysbiosis.

Currently, we are witnessing an explosive growth in interest in using the microbiota and interlinked cascades as a target for therapeutic interventions, including direct microbiome targeting, the attenuation of toxic metabolite-induced damage, the modulation of intestinal immunity, and downstream inhibition of systemic inflammatory pathways.

\textbf{Objective:} In this brief review, modern strategies of microbiome-based therapies for the prevention and treatment of CVD are classified and discussed from the perspective of personalized medicine.

\textbf{Keywords:} Gut microbiome, trimethylamine-N-oxide, atherosclerosis, heart failure, CVD, dysbiosis.

\section{1. INTRODUCTION}

The history of investigating the interaction between the gut microbiota and the human body, as well as the potential therapeutic use of gut flora, stretches over many centuries \cite{1}. At present, we are observing a new wave of interest in the microbiota, driven both by the enclosing of practice, the gut microbiome has been recently specific molecular and immune mechanisms involving a host-microbiome interface and by the results of clinical studies revealing the significance of the microbiome in the prognosis of many diseases. In developing tools that allow for the fast translation of fundamental findings into clinical implicated as a novel therapeutic target along the “gut-immunity-vessels-heart” axis. In recent years, dozens of studies devoted to the impact of the microbiome on CVD have been conducted and a number of excellent reviews have been written \cite{2-5}.

A series of recent experiments show that, from the point of view of the pathogenesis of CVD, the bacterial genome can be regarded as an “extension” of the human. We have now started along the path to “metagenomic” interventions, which consider not only the (epi)genetic and proteomic disease background but also characteristics of microbiome and immune system responses, as well as type of diet.
Table 1. Alterations in the gut microbiome composition in patients with different forms of CVD (16S rRNA – 16S ribosomal ribonucleic acid).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study/Methodology</th>
<th>Changes in the Microbiome in Patients with Disease vs. Healthy Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable CAD</td>
<td>16S rRNA gene sequencing [10]</td>
<td>↑ Bacteroidetes (Bacteroides + Prevotella) ↓ Lactobacillales</td>
</tr>
<tr>
<td>HF</td>
<td>Microbiological tools (BBL Crystal Identification System) [11]</td>
<td>↑ Campylobacter spp. ↑ Shigella spp. ↑ Salmonella spp. ↑ Yersinia enterocolitica ↑ Candida spp. Of note, the mentioned differences were more pronounced in patients with more severe HF</td>
</tr>
</tbody>
</table>

In the current article, we would like to discuss current data on the interplay between the microbiome and its metabolites and the cardiovascular system from the perspective of personalized medicine. Whereas other authors have mainly concentrated on fundamental issues and clinical trials, we focus on potential therapeutic targets and further perspectives on a tailored approach to the modification of the gut microbiome and triggered pathogenic cascades.

2. THE GUT MICROBIOTA IN CARDIOVASCULAR DISEASES

2.1. Investigating the Gut-microbiome-immunity-vessels Axis: Where are We now?

The search for novel links and targets in CVD pathogenesis, inspired by a significant residual risk of complications in well-treated patients with atherosclerotic heart disease, is not fully explained by conventional risk factors [6].

The idea that the microbiome, the immune system and vessels are tightly interconnected in a single pathogenic continuum was based on several solid facts.

- It is well known that patients with inflammatory bowel disease have markedly increased CVD complications, instead of a low profile of conventional risk factors [7].
- The gut microbiota has a key role in maintaining our immune system [8]. In turn, immune system activity and low-grade inflammation become central players in the pathogenesis of metabolic disorders and atherosclerosis, both in the early and in the advanced stages [9].
- Thus, gut microbiomes of patients with coronary artery disease (CAD) [10], heart failure (HF) [11] and arterial hypertension (AH) [12] significantly differ from those of healthy individuals.
- The transfer of the pathogenic microbiota in biological models accelerates atherosclerosis and metabolic disorders [13].

Due to extreme microbiome complexity and diversity, even in healthy people, resulting in difficulties in the determination of cause-effect relationships, we are still far from a clear understanding of specific microbial patterns promoting different forms of CVD.
Nevertheless, at present, we can highlight the gut microbiome alterations that are most likely linked to heart disease progression. Among the most important are: an increase in the Firmicutes/Bacteroidetes ratio [14] and an expansion of several Clostridia clusters [15]; other changes, in connection with specific pathologies, are listed in Table 1.

An altered microbiome affects the heart and vessel walls in three major interconnected ways, as shown in Fig. (1): immunity-dependent, metabolite-mediated and (still debated) direct, caused by microbe translocation from the gut to the vessel wall.

2.2. Intestinal and “Systemic” Immunity in CVD

Bacterial lipopolysaccharide (LPS, endotoxin) is a strong activator of toll-like receptors (TLR) 2, 4, 9 and NF-κB proinflammatory signaling in various cells [17]. Epidemiologic studies have shown that endotoxia constitutes a strong risk factor in early atherogenesis, with subjects with LPS levels beyond 50 pg/ml (90th percentile) having a threefold-higher risk of overt atherosclerosis [18]. In addition to LPS, there are many other capsule-derived compounds (e.g., lipoproteins, peptidoglycans and flagellins), which can activate innate inflammatory pathways [5].

It has recently been demonstrated that specific microbial species are associated with a differentiation of specific subpopulations of T-cells in the intestine. Effector T-cells may be trafficked from the gut to the vessel wall, promoting atherosclerosis [15].

It has been powerfully described that T-cells from the small intestine are also trafficked to the brain and enhance ischemic neuroinflammation. Antibiotic-induced alterations in the intestinal microbiota suppress the trafficking of effector T-cells from the gut to the leptomeninges, resulting in neuroprotection [19].

Consequently, it is very difficult at present to differentiate systemic effects of such proinflammatory substances from a tiny local influence on the intestinal immune system, which, in turn, implements different downstream effects in the myocardium and vessel wall.

2.3. “Leaky Gut” and Vascular Microbiome

Various factors trigger an increase in gut permeability and mucosal inflammation, either directly or due to
influence on the gut microbiota [3]. The “leaky gut” state may appear in patients with severe HF, as well as those with metabolic diseases, such as obesity and diabetes mellitus [20]. In such situations, toxic substances, such as endotoxin, indoxyl sulfate or para-cresyl sulfate [21], as well as microbes and viruses, can leak out of the intestine, raising the “vascular microbiome” [22]. Interest in investigating the direct participation of microbes in atherogenesis was noticeably extinguished after an unsuccessful trial of azithromycin in secondary CVD prophylaxis [23]. However, interest is on the rise again, due to emerging microbiological technologies and new evidence of the non-sterility of our vessels [22].

Although it has been present in systemic circulation in minor concentrations for a long time, LPS could play a crucial role in heating-up low-grade systemic inflammation [20], which, in turn, is considered as the cornerstone of atherosclerosis development and progression [24].

2.4. Microbiota-generated SCFA and Metabolic and CVD

SCFAs (acetate, butyrate, propionate) are small, metabolically active signaling molecules, which are produced by the gut microbiota. Acting mainly through G-protein coupled receptors (GPCRs), which are ubiquitous in the body, they possess many different effects. Gut and fecal SCFA levels are increased in human obesity [25]. While some researchers suggest that SCFAs may increase energy gathering in the small intestine, stimulate de novo lipogenesis and glucogenesis, and promote the development of obesity, other authors suggest that they could increase energy expenditure and the synthesis of hormones with anorexic properties, as well as improve appetite regulation [26].

The contribution of SCFAs to the development of CVD is currently being actively studied. The activation of GPCR 43 by SCFAs, leading to systemic inflammation, could promote atherogenesis, while GPCR 41 stimulation increases sympathetic activity and blood pressure [4].

2.5. TMAO: Offender or Witness?

The strong association between microbe-generated metabolites and CVD was primarily highlighted by using metabolomic tools to compare small molecule profiles of plasma in a large clinical cohort [27]. One of these, TMAO, mainly produced by the flavin-containing monoxygenase 3 (FMO 3) liver enzyme from the microbe-generated precursor, trimethylamine (TMA), was designated as a key unit in bridging dysbiosis and atherosclerosis [4, 28]. Metabolic pathways for the production of TMAO are shown in Fig. (2).

TMA is produced by minor gut flora, which cannot be caught by 16S rRNA gene sequence profiling, while specific strains involved in its synthesis have only been identified very recently. Most likely, it comprises Clos-
tridium XIVa strains and the Eubacterium sp. strain AB3007 [30].

Several well-designed prospective randomized controlled trials (RCTs) have shown that elevated plasma levels of TMAO are strong and independent predictors of the risk of major adverse cardiovascular events in stable CVs [13]. In a cohort of patients with suspected acute coronary syndrome (ACS, n=530), the elevated plasma TMAO level (fourth quartile) at presentation was independently associated with a 6.3-fold higher risk of major adverse cardiac events over the first 30 days and a 1.8-fold higher risk in longterm period (seven years of follow-up) [31].

The evaluation of TMAO among subjects presenting with suspected ACS helps in risk reclassification, especially in patients initially presenting with negative troponin and misclassified as “low risk” by standard models. In this respect, the use of TMAO as a novel point-of-care biomarker for patients with acute chest pain was recently proposed [32].

There are some counterarguments regarding the toxicity of TMAO based on its abundance in seafood, the high consumption of which is considered to be cardioprotective. This suggests that TMAO may act as a disease marker, rather than a direct cause [33].

It should be emphasized that the overt proatherogenic properties of TMAO have been established in many experimental works [34]. In particular, TMAO upregulates the macrophage scavenger receptor (sCr, CD 36) and suppresses reverse cholesterol transport, which hastens the formation of foam cells [35]. TMAO also directly enhances human platelet responsiveness to multiple agonists, thereby increasing thrombosis risk [36].

We suggest that the way in which we acquire TMAO matters. The detrimental effects of high concentrations of TMAO in the plasma of seafood lovers could be counterbalanced by the multitude of protective properties found in the “fruits of the sea”. Especially when consumed as part of a Mediterranean diet, seafood could beneficially impact the gut microbiota. At the same time, the unexpectedly high impact of TMAO levels caused by dysbiosis on CVD prognosis allows us to suspect the presence of a “false bottom”, involving multiple confounders. Some of them, such as immune-mediated mechanisms, could be much worse for cardiovascular health than TMAO.

2.6. Microbiota and HF with Preserved Ejection Fraction (HF-PEF)

A systemic proinflammatory state and coronary microvascular endothelial inflammation play a central role in the early stages of the pathogenesis of HF-PEF, followed by diffuse myocardial fibrosis [37]. New microbiota-dependent proinflammatory pathways ideally fit into this concept. Recent findings suggest that dysbiosis could make a contribution to HF progression, possibly through TMAO-mediated extracellular matrix overproduction, leading to adverse cardiac remodeling [38]. Elevated TMAO levels have been found in patients with HF, and a higher plasma TMAO level has been associated with a 3.4-fold increase in mortality risk [39].

3. MICROBIOME-BASED THERAPEUTIC INTERVENTIONS

At present, we observe a serious degree of enthusiasm among various scientific groups concerning the use of the microbiome as a novel therapeutic target in the treatment of CVD [14, 40].

Gut microbiome-driven specific strategies in CVD management are briefly summarized in Table 2.

Designated therapeutic interventions include: direct microbiome targeting, the attenuation of toxic metabolite-induced damage, the modulation of intestinal immunity, and the downstream inhibition of systemic inflammatory pathways.

3.1. Modification of the Microbiome

The treatment of dysbiosis and the modulation of the composition of the intestinal microbiota by using probiotics for the prevention and treatment of CVD seem to be the simplest approach. The addition of healthy food [3] and physical activity [41], which affect the gut microbiota, may also be helpful.

A reduction in the intake of red meat and eggs, which results in TMAO precursors, such as L-carnitine and choline, represents a potential approach to decreasing TMAO levels. On the contrary, a meta-analysis of 13 controlled trials showed that L-carnitine administration is associated with a 27% reduction in all-cause mortality and a 65% reduction in ventricular arrhythmias in patients with MI compared to controls [53]. When interpreting these results, it should be considered that the effects of prolonged exposure to L-carnitine and its administration in acute cases may be diametrically opposed.

Probiotics may suppress pathogenic flora, decrease systemic inflammation and positively modulate into the innate immunity pathways [54]. Beneficial effects of probiotics in an MI and HF rat model [42] and in chronic systolic HF in humans [44] have been demonstrated.

However, the effectiveness of the long-term colonization of an established gut ecosystem by newly introduced (non-pathological) strains are still being debated [55]. The use of fecal microbiota transplantation was

<table>
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<tr>
<th>Strategy</th>
<th>Intervention</th>
<th>Preclinical and Clinical Trials or Concept</th>
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<tr>
<td>Microbiome modification</td>
<td>Dietary modulation: nutraceuticals and precision nutrition</td>
<td>A number of RCTs investigating dietary interventions have shown that healthy diets are linked to gut microbial changes, which, in turn, are associated with health benefits [3]. Ongoing RCTs on dietary interventions to decrease TMAO levels are of particular interest (NCT02016430).</td>
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<td></td>
<td>Physical activity</td>
<td>A study involving mice showed that positive preconditioning for MI by exercise training to some extent could be explained by altering the gut microbiota [41].</td>
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<td></td>
<td>Probiotics</td>
<td>A rat model of HF, associated with MI probiotic administration, improved systolic and diastolic left ventricular functioning [42]. The possibility of decreasing LDL cholesterol levels by probiotic use in humans was confirmed in a meta-analysis [43]. S. boulardii administration was associated with endothelial function improvement and a decrease in hsC-RP levels in one RCT, which included 20 patients with chronic systolic HF [44]. Use of genetically engineered probiotics (for instance, with an ability to detoxify bacterial LPS) as a novel intervention strategy [14]. Use of specific bacteriocin-producing bacterial strains to promote resistance against the colonization of the gut with pathogenic flora (C. difficile), as part of “precision microbiome reconstitution” [45].</td>
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<td>Antibiotics: systemic</td>
<td>Only one RCT is available showing no effect of azithromycin on the secondary prevention of coronary heart disease [23].</td>
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<td>Antibiotics: selective decontamination of the digestive tract (SDD)</td>
<td>Peroral vancomycin associated with a reduction in myocardial infarct size in a rat ischemia reperfusion model [46]. SDD demonstrated an anti-inflammatory effect among a small cohort of stable patients with severe congestive HF; clinical endpoints were not evaluated [47].</td>
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<td>Fecal microbiota transplantation</td>
<td>Transplantation of fecal microbiota from healthy lean humans to obese patients with insulin resistance was associated with the enhancement of whole-body insulin sensitivity in the recipients [48].</td>
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<td></td>
<td>Keeping healthy microbiota unaltered</td>
<td>No studies have been found. A preventive approach considered the athero-protective properties of a normal microbiota and the negative consequences of non-rational antibiotics use [14].</td>
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<tr>
<td></td>
<td>Attenuation of production of toxic microbiome-linked metabolites</td>
<td>Peroral uremic toxin adsorbents</td>
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<td>Therapeutic apheresis of endotoxin</td>
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(Table 2) contd....
3.2. Attenuation of Damage Induced by Microbiome-derived Toxins and Metabolites

The second mainstream of microbiome-based interventions embraces the attenuated production of toxic microbiota-generated substances or their metabolites. Simple oral charcoal adsorbents are utilized in some hospitals to remove uremic toxins (most of them are microbe-generated) in patients with advanced CKD. Adsorbent AST-120 was found to be effective in the prevention of LV hypertrophy and cardiac fibrosis in a rat model of CKD [49].

The removal of circulating LPS seems to be a tempting idea, but this approach is limited in view of the lack of convenient therapeutic systems for long-term use [50].

Considering the direct detrimental cardiovascular effects of TMAO, the possibility to decrease its levels via the inhibition of microbial TMA-lyase is now recognized by some authors as an approach that could “revolutionize the preventive treatment” of atherosclerotic cardiovascular disease [57]. In fact, inhibitors of TMA-lyase have already been developed and their oral administration has been found to markedly slow down atherosclerosis progression in mice. Regardless of the possibility of translating this approach into clinical practice and strengthening the effect in humans, its influence only extends to microbiota-generated TMA, which is converted into TMAO in the liver. However, nothing can be done in this regard with TMAO from natural sources, such as frutti di mare contains substantial amounts of “pure” and well-adsorbed TMAO [33].

3.3. Modulation of Intestinal Immunity

The modulation of intestinal immunity or the induction of oral tolerance affecting systemic immune responses, including the function and quantity of Tregs and tolerogenic DCs, could be a novel strategy for preventing atherosclerotic CVD [15]. Progress in this field is driven mainly by scientists working in the field of cancer immunology. Current knowledge about immune checkpoints and drugs affecting them is rapidly informing other medical fields, such as rheumatology [58],

<table>
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<tr>
<th>Strategy</th>
<th>Intervention</th>
<th>Preclinical and Clinical Trials or Concept</th>
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<tbody>
<tr>
<td>Decrease in TMAO level via inhibition of intestinal TMA-lyases suppressing microbial TMA formation</td>
<td>Oral administration of 3,3-dimethyl-1-butanol (a structural analogue of choline), in a mice model suppressed microbial TMA production, lowered plasma TMAO levels, and interrupted atherogenesis against the background of a pro-atherosclerotic diet without apparent side effects [51].</td>
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<tr>
<td>Modulation of intestinal immunity</td>
<td>Induction of oral tolerance influencing Tregs and DCs possibly resulting in the attenuation of “pro-atherogenic” T-cells</td>
<td>Oral administration of anti-CD3 antibody and active vitamin D3 induces Tregs and tolerogenic DCs in mesenteric lymph nodes [15].</td>
</tr>
<tr>
<td>Modulation of intestinal immunity</td>
<td>Modulating specific immune checkpoints to stop microbiome-driven low-grade inflammation of vessel wall and plaque</td>
<td>Inhibiting the migration of effector T-cells from the intestine to plaque proposed in [15]. No data available on ongoing studies.</td>
</tr>
<tr>
<td>Downstream blockage of systemic immune and inflammatory mechanisms</td>
<td>Anti-inflammatory therapy affecting innate immunity, in particular, targeting the interleukin-1β pathway</td>
<td>An RCT involving canakinumab conducted on post-MI pts showed positive results, based on hard endpoints [52].*</td>
</tr>
</tbody>
</table>
such that cardiology could benefit from this knowledge in the future.

3.4. Downstream Inhibition of Systemic Inflammatory Pathways

For many decades, the systemic inflammation-centered theory of atherosclerosis (and also HF-PEF) has remained at the virtual stage for clinicians. It has only been translated into real practice with regard to some of the pleiotropic effects of statins, which sometimes have been difficult to distinguish from lipid-lowering dependency. Published in 2017, the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) results confidently demonstrated that the inhibition of IL-1β with canakinumab among patients with a prior MI substantially lowered the inflammatory biomarkers hsC-RP and IL-6 without any beneficial impact on the lipid profile [52]. This effect was translated into a statistically significant decrease in the rate of cardiovascular endpoints (↓ 15% in primary and ↓ 17% in secondary). Although the authors of the study did not comment on possible links with the microbiota, their findings could be interpreted as an illustration of the successful downstream blockage of systemic immune and inflammatory mechanisms, which are misbalanced by an altered microbiota and its metabolites. This could also be regarded as an example of what cardiologists can currently offer in order to fix a misbalanced “microbiota-gut-immunity-vessels-heart” axis.

4. PERSPECTIVES ON THE PERSONALIZED APPROACH FOR MICROBIOME-BASED THERAPEUTIC INTERVENTIONS

When choosing a specific therapeutic intervention for a stable cardiovascular patient, the following factors are ordinarily taken into consideration in real-world clinical practice:

- Symptoms, signs, various anamnestic data and definite clinical diagnosis
- Instrumental and laboratory findings
- Suggestions about prognosis and expected effect of treatment (risk-to-benefits ratio, in the best case, evidence-based)
- Psychological factors (patient preferences) and financial issues

In the era of personalized medicine, we can ensure that our decisions are much more accurate by engaging the following information in such a model:

- Levels of biomarkers with well-known clinical significance
- Real-time measurements of various parameters gathered by wearable or invasive sensors of hemodynamics and electrical activity of the heart

The use of data on lipidomics, metabolomics and proteomics [59] and their analysis by machine learning applications for clinical decision-making [60] are on the horizon.

It should be noted that the evaluation of the microbiome is not included in the battery of pharmacogenetic tests today.

But, using this “conventional precision” approach means that we deal with a holobiont (e.g., a shared human and microbial ecosystem), rather with an individual.

As shown above, the effects of the intestinal microbiota on the development and prognosis of CVD are significant, such that they can no longer be neglected. Therefore, “microbiome analytics” should become one of the integral parts of upcoming “metagenomic” cardiovascular medicine.

We should speculate about what specific microbiome-derived parameters and biomarkers will be possible to analyze, and how that could change clinical practice in the near future?

Firstly, there is fecal microbiome analysis, possibly using 16S rRNA gene sequencing. The observed alterations in the composition of the gut microbiota may lead to personalized non-pharmacological treatments [61], the administration of specific probiotics or SDD, along with recolonization involving microbes with beneficial properties. Such transferred microorganisms could be genetically modified according to the supposed resistance of the pathological microenvironment, which they must overcome. The level of success of the colonization could be controlled by repeated stool analyses.

Secondly, there is a need to assess the levels of biomarkers for dysbiosis, starting with LPS and TMAO. In this future, this could include a broad spectrum of microbiome-generated substances (now known as “uremic toxins”). This kind of evaluation could be particularly relevant to intermediate risk patients as it could possibly re-stratify them into high- and low-risk groups. Knowledge of a significant increase in levels of TMAO or LPS in severe- or very-high-risk patients may indicate very poor prognosis, thereby mobilizing the medical team to reinforce the therapy. Currently, there is no reason to recommend “direct” methods of detoxication in such situations (e.g., to remove endotoxin by apheresis); however, specific pre-oral therapies, which are currently being developed, such as in-
hibitors of intestinal TMA-lyases, could be beneficial in selected patients.

Thirdly, analysis of the subpopulations of T-cells in atherosclerotic plaques, extracted during surgical procedures or even from the peripheral blood, could possibly help to determine patient populations that could benefit from exposure to specific immune checkpoint modulators.

Finally, we are now able to switch from a “personalized” approach, in the sense of a deep analysis of a patient’s exome to “metagenomic” approach, thereby implying knowledge about the interference of the host exome with microbial genomes. For example, if we plan an intervention to reduce the levels of uremic toxins by using the “metagenomic” approach, we should not only analyze the patient’s dietary pattern (e.g., consumption of seafood) and the levels of interested toxins (e.g., TMAO) in the blood, but also identify producers of toxins or their precursors (e.g., TMA) in the intestine, then correlate all this information with the activity of the hepatic monooxygenases (e.g., polymorphisms of the FMO 3 gene [62]). Such a “metagenomic approach” could reveal completely different clinical scenarios: in some cases, the use of inhibitors of microbial TMA-lyase may be beneficial; in others, an increase in TMAO may be treated as an epiphenomenon, such that its reduction will be clinically meaningless.

CONCLUSION

The fine tuning of the microbiota-gut-immunity-vessels-heart axis represents a novel trend in cardiovascular medicine. Notwithstanding the fact that this field is fruitful in terms of biomarkers and specific targets, to date, they have not been included in the context of personalized medicine. The key challenges include the lack of a clear understanding of the relationship between specific microbiome alterations and enhance systemic inflammation, substantial uncertainty in the area of intestinal immune mechanisms, as well as the effects of immune checkpoints’ modulation in the cardiovascular system.

In this article, we have tried to summarize the current microbiome-based approaches for cardiovascular health improvement. We suggest that interventions in microbiome modulation to improve cardiovascular health will gradually become more personalized, starting with diet and microbiota modification, with consideration given to individual microbiome features and levels of microbiota-generated substances and their metabolites. Broad downstream blockage of systemic inflammation (e.g., via inhibition of IL-1β) could be another advantageous strategy before more specific “microbiota-related” immune checkpoints are discovered and tested in clinical studies. In the future, the “metagenomic” approach, which integrates information about interlinked microbiomes and patient exomes, may reveal a conceptually new field for tailored medical interventions, focused both on the prevention and on the treatment of acute and chronic CVD.

LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AH</td>
<td>Arterial Hypertension</td>
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<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<td>CVD</td>
<td>Cardiovascular Diseases</td>
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<td>FMO</td>
<td>Flavin-containing Monooxygenase</td>
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<td>GPCRs</td>
<td>G-protein Coupled Receptors</td>
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<td>HF</td>
<td>Heart Failure</td>
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<td>HF-PEF</td>
<td>Heart Failure with Preserved Ejection Fraction</td>
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<td>HT</td>
<td>Hypertension</td>
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<td>LPS</td>
<td>Lipopolysaccharide</td>
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<td>LV</td>
<td>Left Ventricle</td>
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<td>MI</td>
<td>Myocardial Infarction</td>
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<td>RCT</td>
<td>Randomized Controlled Trial</td>
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<td>rRNA</td>
<td>Ribosomal Ribonucleic Acid</td>
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<td>TLR</td>
<td>Toll-like Receptor</td>
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<td>TMA</td>
<td>Trimethylamine</td>
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<td>TMAO</td>
<td>Trimethylamine-N-oxide</td>
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CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES


