

Human Gut Microbiota in Cardiovascular Disease

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ABSTRACT

The gut ecosystem, termed microbiota, is composed of bacteria, archaea, viruses, protozoa, and fungi and is estimated to outnumber human cells. Microbiota can affect the host by multiple mechanisms, including the synthesis of metabolites and toxins, modulating inflammation and interaction with other organisms. Advances in understanding commensal organisms' effect on human conditions have also elucidated the importance of this community for cardiovascular disease (CVD). This effect is driven by both direct CV effects and conditions known to increase CV risk, such as obesity, diabetes mellitus (DM), hypertension, and renal and liver diseases. Cardioactive metabolites, such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFA), lipopolysaccharides, bile acids, and uremic toxins, can affect atherosclerosis, platelet activation, and inflammation, resulting in increased CV incidence. Interestingly, this interaction is bidirectional with microbiota affected by multiple host conditions including diet, bile acid secretion, and multiple diseases affecting the gut barrier. This interdependence makes manipulating microbiota an attractive option to reduce CV risk. Indeed, evolving data suggest that the benefits observed from low red meat and Mediterranean diet consumption can be explained, at least partially, by the changes that these diets may have on the gut microbiota. In this article, we depict the current epidemiological and mechanistic understanding of the role of microbiota and CVD. Finally, we discuss the potential therapeutic approaches aimed at manipulating gut microbiota to improve CV outcomes. © 2024 American Physiological Society. *Compr Physiol* 14:5449-5490, 2024.

Didactic Synopsis

Major teaching points

- Multiple lines of evidence suggest that the bidirectional interactions between microbiota and the human host are important for both direct and indirect processes affecting cardiovascular health.
- Loss of balanced microbiota composition (dysbiosis) is seen in CVD and conditions with increased CVD risk such as DM, hypertension, obesity, and NAFLD. Dysbiosis is not limited to the colon but can also occur in the small intestine and oral cavity.
- Microbiota effect CVD in multiple ways, including production of cardioactive metabolites (such as TMAO, SCFA, and UT), inducing local and systemic inflammation (directly or by LPS production), and competition with beneficiary microorganisms.
- Altering the gut microbiota to improve CV health is a compelling approach, backed by evidence of reduced risk seen with Mediterranean and low red meat diets. Specific treatments with dietary supplements and specific inhibitors may allow more feasible ways to restore beneficiary microbiota and reduce CVD risk.

Introduction

The importance of the bacterial populations in the gastrointestinal (GI) tract for bile acid and vitamin K metabolism has been understood for many years. However, the human gut microbiota is an extremely complex ecosystem containing bacteria, archaea, viruses, protozoa, and fungi (49), with a total number of organisms estimated at approximately 10^{13} to 10^{15} (104, 402, 458). This staggering number and diversity of the gut microbiota suggest that multiple additional interactions may affect other processes in health and disease. The immense number of colonizing organisms together with evidence of multiple interactions between the host and microbial communities inspired the coining of the

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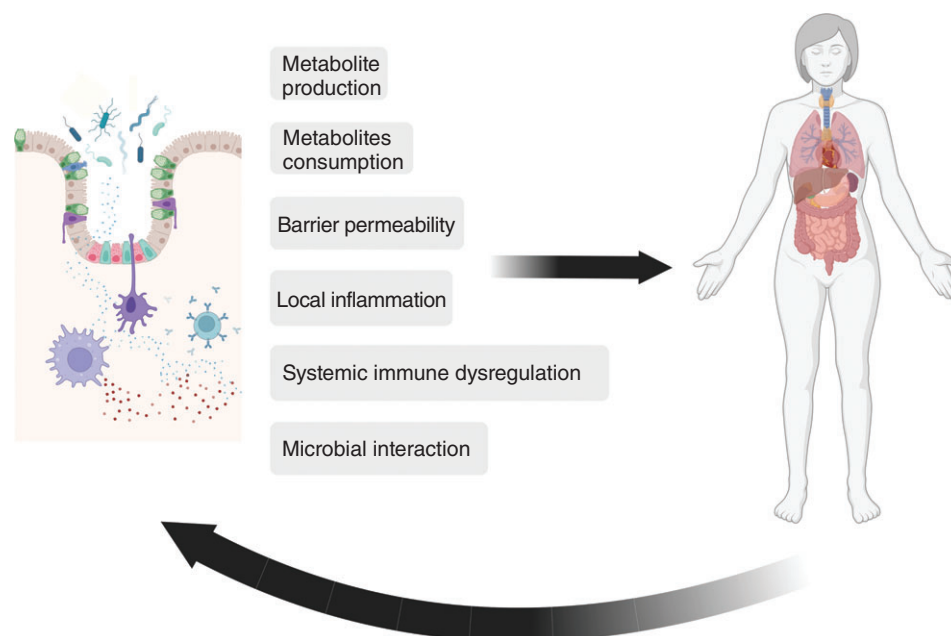


Figure 1 Microbiome-host interactions. Reciprocal interactions between organisms populating the human gut and the host.

term meta-organism. To date, most studies have focused on bacteria, partly due to historical methods relying on cultures for strain identification as well as due to limited data on virus/phage diversity. Based on these methods, gut bacteria seem to be composed mostly by Bacteroidetes, Firmicutes (especially Clostridia species), Actinobacteria, Proteobacteria, and Verrucomicrobia (59) families. However, this initial model is oversimplistic as the number and diversity of microbiota make it difficult to isolate specific interacting pathways. The task is further complicated by the fact the GI tract contains significantly different environments, ranging from the open oral cavity to the acidic stomach followed by aerobic conditions in the small intestine and the anaerobic colon. These differences result in each environment containing significantly different microorganism populations (262). Other factors, including the possibility that a rare population of microorganisms may be responsible for major effects, long-term temporal population changes, and changes due to interaction with host comorbidities (66, 320), make the task even more daunting. Additionally, recent sequencing data showed that even within the same species, differences in transcription and protein expression can correlate with various disease states (66, 473, 591).

In spite of the abovementioned difficulties, substantial advances in the field have revealed interactions between gut bacteria and multiple conditions, including DM, obesity, hypertension, dyslipidemia, Parkinson's disease, and various inflammatory diseases (65, 428, 533, 604). Observations that diet is a major component affecting many CV risk factors make gut microbiota's integral role in cardiovascular disease (CVD) unsurprising. Indeed, correlative studies

have discovered direct and independent interactions between microbiota and CVD, including heart failure (HF), atherosclerosis, and atrial fibrillation. Mechanistical studies in model animals and clinical trials have elucidated several pathways in which microbiota influence the CV system, including toxic metabolites, inflammatory modulation, and platelet activation. Therefore, gut microbiota may interact with the host through several mechanisms, including (Figure 1):

- Production of absorbable metabolites/toxins
- Modification/removal of metabolites from the GI tract
- Interaction with gut barrier to change permeability properties
- Modulation of systemic inflammatory state by direct translocation
- Modulation of local inflammatory response
- Intramicrobiota interaction can change composition/diversity.

In this article, we present the recent advances in our understanding of the interactions between gut microbiota and CV disease.

Dysbiosis Clinical Correlation

Changes in diet, host disease, and other conditions can result in significant changes in microbiota composition. These changes may cause beneficiary species to diminish, while unwanted species may thrive, prompting the introduction

of the term dysbiosis. This imbalance between microbial communities prompted the search for bacterial changes in specific diseases to better understand the role of microbiota in each condition.

Gut microbiota

Difficulties in obtaining small-intestine samples require that most gut microbiota analysis is performed by collecting data from fecal matter. The staggering mass of fecal bacteria resulted in initial attempts to find changes in whole populations. Analyzing diversity indexes, such as alpha (microbiome diversity applicable to a single sample), beta (differences between populations), and the Shannon–Wiener index (diversity of species in a community), gave mixed results in CVD patients (236). Being the most abundant, Firmicutes (F) and Bacteroidetes (B) species, their ratio (F/B ratio) was found as a general indicator of the gut microbiota state. Changes in F/B ratio were found to correlate with CVD; however, there seem to be mixed results, probably due to the inherent generalization of this ratio (377, 546). Multiple species-level studies have found association between bacterial families and CVD risk factors, such as glucose and lipid abnormalities (134, 323, 446, 515, 604), hypertension (107), chronic kidney disease (CKD) (185), and inflammation (537). Case-control studies comparing CVD patients found differences in species, such as Lactobacillales, Bacteroidetes, and Enterobacteriaceae (117, 205, 226). Recently, sequencing results of 1023 samples from standardized diet participants in the Personalized Responses to Dietary Composition Trial (PREDICT 1) study (30) demonstrated concordance between specific microbial patterns and biomarkers known to correlate with cardiometabolic risk and even a composite of the atherosclerotic CVD score (21). As changes in dietary intake are known to result in a shift in microbiota population (172, 252, 592), the increased CVD risk associated with consuming certain foods (243, 256, 381, 515) may be partially linked to changes in microbiota.

Indeed, Francesco Asnicar et al. classified foods using several indexes assessing plant, animal, and Mediterranean diet sources to better understand the effect of dietary sources on microbiota (21). Unprocessed plant-based diets and animal diets based on eggs and fish were correlated to butyrate-producing species *Roseburia hominis*, *Agathobaculum butyriciproducens*, *Faecalibacterium prausnitzii*, and *Anaerostipes hadrus* as well as uncultivated species, predicted to have similar metabolic capability, *Roseburia* bacterium CAG:182 and Firmicutes bacterium CAG:95 (21). While *Clostridium* species (*Clostridium innocuum*, *Clostridium symbiosum*, *Clostridium spiroforme*, *Clostridium leptum*, and *Clostridium saccharolyticum*) were correlated with animal diets based on red meat, dairy desserts, and processed foods (21), Mediterranean diet, known for its cardioprotective properties, was negatively correlated with the abundance of *Ruminococcus torques*, *Clostridium leptum*, and *Collinsella aerofaciens* species (546), all of which are known to be

associated with western diets (11, 150). In contrast to these results, a recent prospective population-based study involving 7211 adults demonstrated that increased Enterobacteriaceae abundance was significantly associated with all-cause mortality [adjusted hazard ratio (HR) 1.16, 95% confidence interval (CI): 1.09–1.25; false discovery rate (FDR) <0.0001] but not significantly with CVD risk (adjusted HR 1.03, 95% CI: 0.91–1.16; FDR = 0.63) (435).

Taken together, it seems that certain bacterial populations are associated with increased CVD risk either directly or by influencing known CVD risk factors, and that this could be mediated in part by dietary consumption patterns. However, further studies are needed to establish the long-term effect of this interaction.

Oral microbiota

Differences in oral bacterial populations have been detected in several conditions, including IBD (495) and hypertension (88). Several observational studies have reported that patients suffering from CVD tend to have worse oral hygiene compared to healthy individuals (83), and that chronic periodontitis is associated with an increased risk of CVD (24, 26, 31, 82, 140, 205, 334, 415, 444, 453). Specifically, the findings of *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* were shown to correlate with CVD (44, 125). Recently, a prospective observational study of 102 CV patients undergoing coronary artery bypass graft (CABG) demonstrated the presence of Saccharibacteria phylum in subgingival samples it was associated with (452). The increased risk may be mediated by increased inflammatory modulation or secondary bacteremia (324, 401). Surprisingly, *Chryseomonas*, *Veillonella*, and *Streptococcus*, both present in the oral cavity, were identified in atherosclerotic plaque samples (248), providing another possible link between periodontitis and increased risk of CVD (555). However, given the existence of multiple shared risk factors between periodontitis and CVD, these studies are only associative and do not yet prove causality.

Another means by which oral bacteria can influence CVD is through the enterosalivary nitrate-nitrite-nitric oxide pathway. In this pathway, dietary nitrate (NO_3^-) is converted to nitrite (NO_2^-) by oral bacteria and is absorbed to serve as a pool for NO generation (304). Multiple studies have demonstrated that reduced oral nitrite production results in increased BP and insulin resistance (148, 240, 304, 522), known CVD risk factors. The identification of specific species has proven more difficult, with *Neisseria flavescens*, *Haemophilus parainfluenzae*, and *Rothia dentocariosa* showing association with reduced CVD risk (147, 148, 169). Recently, new analysis of the prospective cohort Oral Infections, Glucose Intolerance, and Insulin Resistance Study (ORIGINS) showed the importance of the balance between nitrite-producing and -reducing oral populations in affecting cardiometabolic risk score including BP and glucose response (147). Furthermore, this may be affected by vegan diet (169).

Given the current state of knowledge, mechanistic studies in animal models and humans are warranted to unravel the complex relationship between periodontitis, alterations in oral microbiota, and CVD and to elucidate specific pathways underlying this interaction.

Atherosclerotic plaque microbiota

Previous reports have identified DNA from *Staphylococcus* species, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Streptococcus* species in atherosclerotic plaques (248, 293), and Proteobacteria and Actinobacteria were recognized in a larger cohort of endarterectomy samples (212). However, no difference in the abundance of these pathogens was detected between symptomatic and asymptomatic patients (212). It is possible that these findings represent bystander findings or DNA fragments from bacteria consumed by immune cells and not viable bacteria (248). In contrast, recent work demonstrated that *Staphylococcus* and *Streptococcus* were enriched in plaque samples from acute coronary syndrome patients, while *Paracoccus* was enriched in samples from patients with chronic coronary syndrome (389). In addition to these populations, certain pathogenic bacteria, such as *Chlamydia pneumoniae*, *Helicobacter pylori*, and *P. gingivalis*, can affect vascular cells and thus contribute to CVD development (555). In spite of all these findings, trials examining the effect of antibiotics did not show any clinical benefits in reducing CV morbidity or mortality (15). Therefore, the direct contribution of bacterial invasion into atherosclerotic plaques is yet to be established.

Cardioactive Gut Biomarkers

An important aspect of host/microbiota interaction is mediated by microbiota-produced metabolites. Indeed, recent data suggest that multiple bacterial metabolites are absorbed into the blood stream and even the CNS, affecting glucose and lipid metabolism (95). However, the gut environment also contains numerous pathogens and unwanted/toxic substances that require multiple lines of defense to ensure that these do not crossover to the systemic circulation. These include mucus lining (42, 209), epithelial barrier, and tight junction integrity (4), followed by vascular endothelial and extensive immune cell populations (338, 481). Indeed, gut barrier integrity is affected by resident lymphocyte and macrophage (94) populations producing IL-22, IL-18, IL-21, and CCL-3, tissue inhibitor of metalloproteinase 2 (73, 206). Importantly, microbiota composition is also a significant aspect of the gut barrier health as conditions favoring certain populations or microbiota-microbiota interactions can reduce unwanted toxins and bacterial populations. This is well demonstrated by observations of impaired barrier function and endotoxemia seen following high fructose (457), high fat (338), and dietary emulsifier intake (present in processed foods) (62, 63). Recent data provided evidence that these interactions extend beyond

the bacterial populations as mucosal fungi were shown to increase the production of IL-22 and strengthen the gut barrier (267). In addition, local inflammatory response and reduced blood perfusion seen in several pathological conditions, such as HF and ischemic heart disease, can compromise the epithelial cell barrier and tight junction integrity (95, 374).

This complex barrier-microbiota interaction results in reciprocal dynamic changes effecting health as demonstrated in type 2 DM and nonalcoholic fatty liver disease (NAFLD) (7, 513, 517). In this section, we review the main gut-related cardioactive biomarkers and their involvement in CVD as well as the recent advances in metabolome screening, identifying additional substances (352) (Figure 2).

Trimethylamine N-oxide (TMAO)

Western diets rich in animal products such as red meat (594) have high content of choline (550), phosphatidylcholine (503), and carnitine (242). These precursors are converted into betaine (550), γ -butyrobetaine (242), and trimethyllysine (288), which is later converted to trimethylamine (TMA) gas by multiple gut bacteria (503, 550). TMA in turn is absorbed into the portal circulation where it is converted into TMAO by hepatic enzyme flavin monooxygenases (FMO—mainly FMO3) (553). TMAO is then extracted by the kidneys (10); hence, reduced renal function results in increased TMAO levels (502). TMAO has been shown to be significantly and independently associated with CVD, atherosclerosis, and all-cause mortality in multiple cohort studies (128, 179, 406, 425, 445, 473). These findings were supported by similar results in animal models (8, 108, 425, 473, 552, 564, 570). In the recent European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC) trial, a prospective study of 25,663 healthy participants with 8-year follow-up, case-control analysis of 908 individuals who developed CVD and 1273 controls with elevated TMAO levels conferred an increased risk for incident CVD development and remained predictive following adjustment for traditional risk factors [odds ratio (OR) 1.58, 95% CI: 1.21–2.06; $P < 0.01$] (501). A recent umbrella meta-analysis of 39,314 participants demonstrated a significant correlation to major adverse cardiovascular events (MACE) even after adjustment for potential confounding factors (HR 1.65, 95% CI: 1.56–1.95; $P = 1.13 \times 10^{-22}$) (274). This correlation was dose dependent (HR 1.11 for each 1 μ mol/liter TMAO, 95% CI: 1.07–1.114; $P = 1.04 \times 10^{-4}$ in three studies). Another meta-analysis, including 12 studies and overall 22,945 participants, showed that elevated TMAO levels had significant association with CVD events (OR: 1.50, 95% CI: 1.26–1.79; $P = 8.0 \times 10^{-6}$) (277). This latest meta-analysis is consistent with previous studies showing significant association of TMAO with CVD (139, 179, 274, 406, 445, 449, 578), MACE (159, 179, 274, 445, 580), and all-cause mortality (128, 445) as well as inflammation (129), hypertension (139), and DM (614). Although the correlation between TMAO and CVD risk remains significant after adjusting for renal function (274), care must to be taken

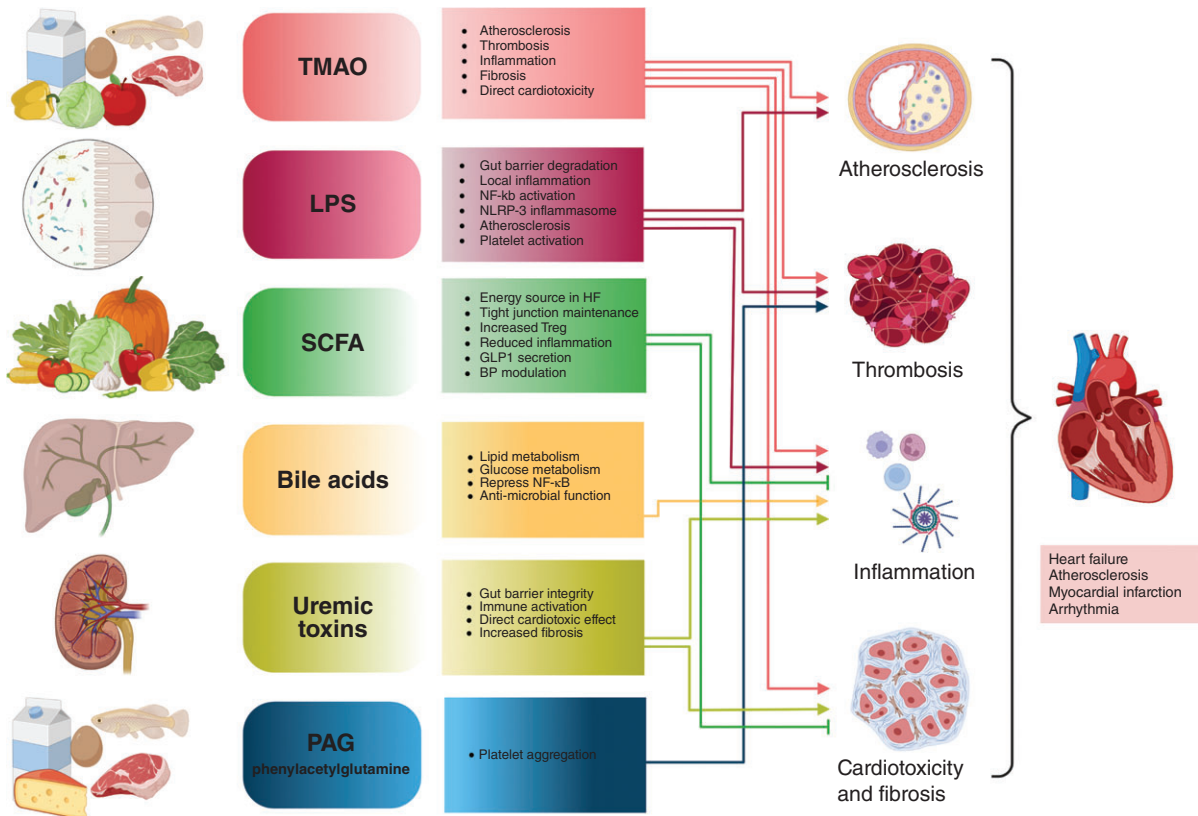


Figure 2 Conditions and metabolites affecting cardiovascular disease. Effect overlaps of bioactive metabolites in both cardiovascular risk factors and processes directly implicated in CVD.

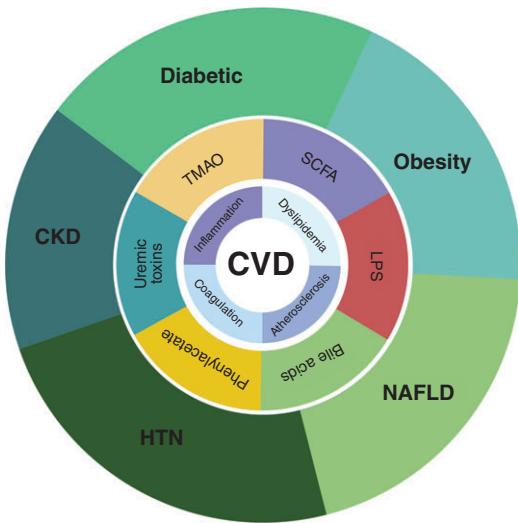


Figure 3 Sources and mechanisms of specific metabolites affecting CVD.

in this population as the effect of TMAO on CVD risk is impaired in patients with reduced renal function (223, 485). TMAO seems to exert its CV effects through multiple pathways (Figure 3). Experiments in mouse models have shown that increased TMAO production due to choline- or

carnitine-rich diet resulted in increased atherosclerotic burden (153), which was mediated by increased cholesterol content in macrophages and foam cell formation (243, 550). TMAO also enhances thrombosis in germ-free mice transplanted with microbial communities possessing high TMA-producing capabilities (611). Furthermore, FMO3 knockout mouse models showed that TMA and TMAO levels augmented thrombotic potential by changing platelet responsiveness and clot formation rates (467, 610, 611). Increased TMAO levels also result in activation of inflammatory processes (456), and the pro-inflammatory mechanism of TMAO (67, 456) may play a crucial role in the acute phase of heart injury. Recent data have shown that in 985 patients hospitalized for acute myocardial infarction (MI) and HF, the TMAO levels correlated with MACE (median follow-up of 716 days) only if high-sensitivity C-reactive protein (hsCRP) levels were above the median level (6.68 mg/liter) (568). This is supported by data showing increased cardiac endothelial inflammation in response to high TMAO levels (489). In addition to these indirect CVD risk accentuation effects, TMAO appears to have direct myocardial effects via inducing hypertrophy and fibrosis (290). TMAO exerts its cardiotoxic effects by activating the Nucleotide-Binding Oligomerization Domain, Leucine-Rich Repeat, and Pyrin Domain Containing 3 (NLRP3) inflammasome pathways (38, 67), resulting in changes in cardiomyocyte mitochondrial

function (307) and actomyosin activity (253). Indeed, mice infused with TMAO showed signs of vascular inflammation with activation of NF- κ B (456). TMA on the other hand can specifically bind olfactory receptor TAAR5 (trace amine associated receptor 5) (543); however, the role of TAAR5 in CVD is not well understood. Metabolically, TMAO may also affect CV health by affecting bile acid metabolism and transport (243) as discussed later.

Increased red meat intake led to increased plasma TMAO levels in feeding experiments (549). However, both meat- and plant-based diets contain an abundance of choline, resulting in similar TMAO production capacities (549). Converting choline or L-carnitine to TMA may be performed by microbiota utilizing three main gene clusters: (i) *cutC/D*, a glycyl radical enzyme and a glycyl radical activating protein (473). (ii) *cutA/B*, a two-component Rieske-type oxygenase/reductase complex (613). (iii) Betaine reductase (116, 499). Studies evaluating TMA production capabilities indicate that the majority of TMA is produced in the more distal gut segments and under anaerobic conditions (241). Indeed, choline conversion is mainly performed by *cutC/D* (424, 425) gene cluster under anaerobic conditions (48). In contrast, conversion of L-carnitine, which is more abundant in red meat, to γ BB and then to TMA may be performed by *CutA/B* but requires oxygen (241, 613). Surprisingly, recent cross-sectional genetic analysis of consecutive fecal and blood samples found only low transcription levels of *CutC/D* or *CutA/B* genes (277). Therefore, the question of the origin of TMA production from L-carnitine in anaerobic conditions has emerged (549). Recent data from a cross-sectional study of 925 metagenomes from 307 healthy men indicate that this conversion may be facilitated by recently identified rare bacteria that were associated with higher TMAO concentrations. These include Firmicutes species, *Clostridium citroniae*, *Clostridium nexile*, *Clostridium clostridioforme*, Clostridiales bacterium 1 7 47FAA, *Eubacterium hallii*, *Eubacterium bifforme*, Erysipelotrichaceae bacterium 21–3, and *R. hominis*, one Bacteroidetes species (*Alistipes shahii*), and one Actinobacteria species (*Eggerthella* unclassified) (277). It should be noted that previous studies have also identified *Clostridium* species to be associated with higher TMAO levels after carnitine challenge (567), and that *Eggerthella lenta* can convert L-carnitine to TMA (277).

TMAO precursors, betaine, γ -butyrobetaine, and trimethyllysine, were also shown to be associated with CVD in a TMAO-dependent manner (288). Prospective 12.5-year follow-up of a 3932 community-based cohort Cardiovascular Health Study (CHS) (133, 511) showed that meat consumption was associated with increased incidence of atherosclerotic CVD (HR 1.15, 95% CI: 1.01–1.30; $P=0.031$, for unprocessed red) and (HR 1.22, 95% CI: 1.07–1.39; $P=0.004$, for total meat), and that this was mediated in part by TMAO and its metabolites, including γ BB (548). These results were further corroborated by another recent prospective study showing that γ BB is associated with MACE after adjusting for known CVD (43). Interestingly, the

authors of this study identified a rare community of *E. timonensis* and its gene cluster, *GbuA*, as an important converter of γ BB to TMA. This finding is supported by the Animal and Plant PROtein and Cardiovascular Health (APPROACH) study (Clinicaltrials.gov, accession no. NCT01427855) (549), a prospective randomized dietary controlled trial showing an increase in *GbuA* gene in samples from subjects consuming red meat as a protein source (43).

Interestingly, recent data showed that red meat consumption is only correlated to increased TMAO levels in the presence of specific bacteria (277). Given the similar choline intake of vegan- and meat-based diets, these findings may explain the difference observed in TMAO levels and CVD risk between studies and between vegans and omnivores (red meat consumers) (43, 241).

Despite the extensive supporting data, recent reports following two cohorts in Norway [WECAC; 4132 patients with suspected coronary artery disease (CAD) of which 74.9% had angiographically significant CAD] and the Hordaland Health Study (HUSK; 6393 community-based subjects) found no significant increase in all-cause mortality (HR 1.04 CI: 0.97–1.12) or CV death (HR 1.03 CI: 0.93–1.13) per one standard deviation increase in log-transformed plasma TMAO levels (WECAC suspected CAD data) with similar results observed in the HUSK community-based data (34) during approximately 10 years of follow-up. These results may be due to the relatively homogeneous study population and heterogeneity in fasting conditions. In addition to these cohort studies, small studies have reported similar results (35, 340, 593), indicating that the lack of association found between red meat consumption and gene transcription levels in high TMAO individuals (277) merits further investigation.

A recent study of 356 healthy participants (aged 18–66) found no significant association between TMAO levels and glucose, insulin, or lipid levels. Furthermore, no correlation was found to inflammatory markers, including CRP, IL1, or IL6 (199). The lack of correlation in this study may be explained by the relatively low TMAO levels in this cohort (199) and the low incidence of CVD in healthy young individuals, thereby making detection highly challenging. The lack of significant association between TMAO and CV risk in healthy subjects has also been observed in other studies (14, 179, 277, 294, 308, 326, 406). Mechanistically, this may be explained by the protein-stabilizing effects of TMAO as suggested by its role in deep sea fish (521). Therefore, the role of TMAO in healthy individuals requires more studies to further understand its importance as a marker or/and a driver of CVD and other diseases.

Lipopolysaccharides

Lipopolysaccharides (LPS), a membrane component of Gram-negative bacteria, are composed of polysaccharides bound to a lipid A portion and are a potent bacterial toxin. LPS can enter systemic circulation by incorporation into gut chylomicron particles and translocation of the gut barrier

(146, 309). Following their entrance to the blood circulation, LPS bind LPS-binding protein and are finally cleared by transfer to hepatic degradation in lipoproteins, primarily LDL (270).

LPS levels have been associated with CKD, DM, obesity, and dyslipidemia (Figure 3) (2, 286). CV manifestations, including AF (378, 602) and atherosclerotic CVD (56, 238, 269), are also associated with increased LPS endotoxemia (Figure 3) (19, 269). High LPS levels were shown to result in increased incidence of MACE in AF patients during a 3-year follow-up period (378, 379). A recent assessment of 1152 plasma samples showed that LPS levels increase with age (602), possibly explaining in part the increased prevalence of AF seen in elderly. Elevated LPS levels are also detected in patients with acute MI compared to patients with stable disease (56), and high LPS levels are even associated with increased CV events after 3 years of follow-up (607). However, further investigation is needed to assess whether the increased levels were a contributing factor for the development of acute MI or a consequence of gut barrier breakdown resulting from impaired cardiac function.

LPS are recognized by toll-like receptor (TLR) on various immune cells, with binding resulting in NF- κ B pathway (297) and inflammatory response activation (20). LPS endotoxemia contribution to atherosclerosis is mediated by multiple pathways, including activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2) (360, 538), resulting in increased oxidized LDL levels, platelet activation through binding to TLR4, TLR2, and TLR9 (249, 250), and activation of plaque macrophages (54). TLR activation plays an important role in NLRP3 inflammasome priming and activation in cardiomyocytes (110). NLRP3 inflammasome activation is seen in both paroxysmal and chronic AF (579) and occurs during MI (469, 518) and HF (563). Interestingly, LPS from different bacteria have altered TLR binding and immune response capacity (531), indicating that different bacteria may elicit diverse responses. Further experimentation is needed to link specific gut bacteria with subtypes of LPS and their specific effect on the CV system.

Short-chain fatty acids

Short-chain fatty acids (SCFA), including acetate, propionate, and butyrate, are mostly produced by gut microbiota in anaerobic fermentation from plant-based fibers (96, 337); however, a small amount can be produced by the human host (384). SCFA are an important energy source, mainly for the large intestine epithelial cells and thus crucial for gut barrier integrity (112). In contrast, healthy cardiac metabolism is largely dependent on energy-rich long-chain fatty acids (LCFA) (433), which are actively transported to mitochondria by carnitine palmitoyltransferase I (CPT1) (272). However, in the setting of HF, there is a significant reduction in LCFA oxidation (344) with a shift toward ketone bodies as an alternative cardiomyocyte energy source (22). Interestingly, emerging data indicates that SCFA are also

an important energy source for the failing heart (52). This may be attributed to the energy-free transfer of SCFA to the mitochondria (60). Indeed, inducing hypoxia by coronary stenosis in porcine hearts resulted in preferential SCFA utilization compared to LCFA (273). This is further supported by observations of reduced CPT1 activity in HF (272).

In addition to providing energy, SCFA have been shown to have positive systemic effects on lipid metabolism, glucose homeostasis, and gut inflammation, thus exerting CV benefits (Figure 3) (244). SCFA-driven anti-inflammatory properties in the gut can be attributed in part to T regulatory (Treg) cell activation (310). In support of this, SCFA supplementation to elastase-induced abdominal aortic aneurysm (AAA) in mice resulted in reduced AAA diameter, which was mediated by colonic Treg recruitment to the affected aorta and reduced inflammation (575). SCFA also play an important role in immune response and cardiac repair following induction of MI in mice (204, 500). Moreover, SCFA have been implicated directly in CVD through improving cardiac stunning in postischemic rabbit models (271) and contractility in murine models (281).

SCFA bind free fatty acid receptors 2 and 3 (FFAR2/3) (585) expressed by multiple organs, including the heart, adipose tissues, and sympathetic neurons (234). In rat models, activation of FFAR2 induces glucagon-like peptide 1 (GLP-1) secretion (77), and FFAR3 knockout results in reduced sympathetic tone and reduced heart rate (235). Collectively, SCFA binding to FFAR2/3 confers a combined cardioprotective effect. In humans, FFAR2 expression on leukocytes has been shown to be reduced in acute ischemic patients (429); however, the direct effect of FFAR2/3 activation in humans still needs further examination. In addition, at least part of SCFA-mediated CV benefit is mediated by affecting the blood pressure (BP) via binding of SCFA to G-protein-coupled receptors, such as olfactory receptor 78 (Olf78) and G-protein receptor 41 (Gpr41) (350, 363). Indeed, Olf78 knockout mice are hypotensive (390), while Gpr41 knockout mice are hypertensive (350). Furthermore, binding of SCFA to Olf78 expressed on vascular smooth muscle cells results in increased vascular resistance, and binding to Olf78 on renal juxtaglomerular cells results in increased renin release leading to hypertension (390). Binding of SCFA to Gpr41, which is also expressed on vascular endothelial cells, results in BP reduction (350, 391).

The contradicting effect of SCFA on BP demonstrated by FFAR2 and FFAR3 activation indicates that the entire molecular effects of SCFA on the CV system are not yet fully understood. Indeed, as overwhelming clinical data are supportive of a cardioprotective role of SCFA, more studies are required to further elucidate the underlying mechanisms, especially in human systems.

Bile acids

Primary bile acids (BA) are produced by the liver and secreted into the duodenum where they are modified by gut

microbiota into a wide variety of secondary bile acids before reabsorption (227). Secondary bile acids can bind to various host receptors, including farnesoid X receptor (FXR), liver X receptor (LXR), pregnane X receptor (PXR), and takeda G-protein-coupled receptor 5 (TGR5) (64, 224, 545). These interactions have been shown to modulate immune responses (193) and lipid and glucose metabolism (75, 157, 163, 224) with potential implications on the CV system (Figure 3). Specifically, fecal BA levels are lower in CAD patients (61), and a recent cohort study demonstrated that among 7438 patients admitted for coronary angiography, the total blood BA levels were lower in confirmed CAD patients and inversely correlated with severity (285). Similar results were reported in another study using stringent enrolment criteria including statin use (355).

FXR is extensively expressed in the heart (33) and may be involved in cardiac fatty acid metabolism (164). Additionally, evidence suggests that FXR activation inhibits IL1 β -induced rat aortic inflammation in an NF- κ B-dependent manner (142). This is supported by data showing reduced atherosclerosis following administration of chenodeoxycholic acid (CDCA) derivatives to apolipoprotein E-deficient (ApoE^{-/-}) mice (168, 175) and the fact that plaque size was increased in compound FXR^{-/-} mice compared to LDL^{-/-} or ApoE^{-/-} alone (168, 175). Furthermore, TGR5 activation in LDL^{-/-} mice resulted in reduced atheroma formation (396). In addition to the effects on the host, bile acid composition impacts microbiota population through its antimicrobial properties (193), creating a feedback loop. Other studies, however, have reported a detrimental effect of BA on CVD (168, 525), which may be due to differential receptor activation by different types of BA. Further studies are warranted to elucidate the role of BA in CVD progression.

Uremic toxins

CVD is a major cause of morbidity and mortality in patients with CKD (207, 414). Multiple studies have found significant correlation between gut microbiota and CKD (519). One of the hallmarks of reduced kidney function is the increased levels of uremic toxins (UT). UT are classified as water soluble, such as phosphor, urea, creatinine, and TMAO; intermediate molecules, such as fibroblast growth factor 23 (FGF23); or protein bound, such as indoxyl moieties, kynurenine, kynurenic acid, *p*-cresyl sulfate, and indole-3 acetic acid (414).

As renal failure progresses, UT levels are increased, resulting in enhanced transfer of urea to the gut (185, 519) and concomitant favoring of gut bacteria expressing urease and tryptophanase (559). Increased urea levels combined with altered microbial composition result in increased levels of indole, ammonia, and ammonium hydroxide. These UT cause gut epithelial barrier disruption (151), which further increases the absorbance of UT and other toxins. Furthermore, dietary intake is important in CKD patients as protein-bound UT and TMAO originate from dietary protein metabolism (414).

Increased phosphate levels are common in renal failure and were shown to increase vascular smooth muscle proliferation and calcification (183), thereby resulting in increased susceptibility to thrombosis (462). This is further highlighted by a positive correlation between high FGF23 and CV mortality among patients undergoing hemodialysis (565). Furthermore, indoxyl sulfate and kynurenine can bind to aryl hydrocarbon receptor (AHR), leading to increased transcription and reduced degradation of tissue factor in endothelial cells (462), thus increasing the risk of thrombosis. UT are also involved in immune modulation (423). Specifically, indoxyl sulfate can induce macrophage activation (348) and increase TNF- α and interleukin-6 (IL-6) secretion (348). *p*-Cresyl sulfate inhibits Th1 lymphocytes and interferon- γ (IFN- γ) production (466) and seems to have a direct cardiotoxic effect (166). Klotho, an antisenescence protein mainly expressed on renal tubular cells and also secreted in a soluble form (257), is reduced in CKD, possibly due to interactions with indoxyl sulfate (576). The role of Klotho in CVD has been demonstrated in mice showing reduced cardiac fibrosis and improved function following recombinant α -Klotho administration (188, 576). Additionally, renal fibrosis secondary to long-standing UT (487) results in activation of renin-angiotensin system (156) and increased oxidative stress both of which contribute to increased CV damage (432). Clinically, a Cohort study of dialysis patients reported that patients with increased indoxyl sulfate, kynurenine, AHR activity and tissue factor had a greater risk of developing arteriovenous fistula thrombosis (246). Interestingly, demonstrating a direct connection of indoxyl sulfate and *p*-cresyl sulfate levels with CV outcomes in human cohort studies has been challenging (283, 461, 572). Further data is thus needed to confirm that the observations seen in animal models can be translated to humans.

Phenylacetate

A remarkable example of the power of unbiased metabolomic research was the confirmation of phenylacetylglutamine (PAG) as an important effector of CVD. PAG, a product of phenylalanine metabolism produced by gut microbiota and the liver (352), was initially shown to be associated with CVD (Figure 3) (392). This was further substantiated by Nemet et al. (352) and Ottosson et al. (369) using larger cohorts. A recent cross-sectional analysis of 956 participants found PAG to be significantly higher in HF patients ($3.322 \mu\text{M} \pm 8.2$ vs. $1.24 \mu\text{M} \pm 1.16$; $P < 0.001$), and that the risk for HF increased significantly with increase in PAG even after adjustment for renal dysfunction (HR 1.8 95% CI: 1.53–2.16; $P < 0.001$) (615). The authors further showed increased risk of a composite of CV death or rehospitalization for each SD PAG (HR 1.48) in a prospective study including 471 patients with chronic HF with reduced ejection fraction (HFrEF) with mean follow-up of 2 years (615). These results confirm data from previous HF studies (498).

Once produced, PAG interacts with α 2A-, α 2B-, and β 2-adrenergic receptors (352), and this interaction results in

increased platelet aggregation (352) elegantly explaining the correlation seen between PAG and atherosclerosis (298). It is worth noting that PAG was associated with multiple disease states, including CKD, and elucidating the mechanism of its involvement is of great interest.

Risk Factors and Comorbidities

Atherosclerosis

Atherosclerosis is a multistep process driven by accumulation of cholesterol under the arterial subendothelial layer followed by oxygenation and inflammatory responses. The continued cholesterol accumulation together with endothelial damage and chronic inflammation result in unstable plaque with increased risk of rupture (342, 561). Association studies have shown an increase in Lactobacillales, *Collinsella*, Enterobacteriaceae, and oral bacteria species with a concomitant decrease in *Bacteroides* and *Prevotella* in patients with CAD (342, 561). In addition, multiple pathogenic microorganisms, including *Cytomegalovirus*, *Chlamydia pneumoniae*, and *Helicobacter pylori* (89, 120, 380, 434), have also been associated with increased plaque formation; however, their implication in chronic CAD is unclear. The role of gut microbiota in atherosclerosis was further supported by multiple murine studies (20, 153, 237, 514). Recent data from 55 patients admitted for coronary intervention undergoing coronary optical coherence tomography (OCT) or intravascular ultrasound imaging (IVUS) showed association of *Bacillus*, *Paraprevotella*, and *Succinatimonas* with higher plaque burden and thin fibrous cap, while *Anaerostipes* and Lachnospiraceae UCG-003 had significant association with favorable plaque features (387).

As inflammation plays a crucial role in atherosclerosis progression (46, 336), early studies have focused on the role of LPS in atherosclerosis. In one study analyzing 2568 CAD-free participants with 10 years of follow-up, high LPS-binding protein levels were found to be significantly associated with CVD (19). Infusion of LPS resulted in accelerated aortic atherosclerosis in rabbits and mice, and this was accompanied by increased inflammatory markers, such as IL-8 and TNF- α , and increased local inflammation (266, 368). Similarly, LPS infusion in ApoE^{-/-} mice accelerated the progression from stable to unstable aortic arch atherosclerotic plaques (201). This effect was mediated by TLR4 because Tlr4^{-/-} ApoE^{-/-} mice had reduced aortic plaque area compared to control ApoE^{-/-} mice (109). Furthermore, LPS injection to ApoE^{-/-} mice resulted in increased TLR4 expression in atherosclerotic plaques with increased leukocyte infiltration and characteristics of unstable plaques, such as increased necrotic cores, collagen digestion, and reduced cap thickness (317). This is supported by data showing that inhibition of TLR4 resulted in better gut mucosal integrity with reduced LPS levels and reduced atherosclerotic size (144). Direct observations by immunohistochemistry of human samples found that TLR4 was

overexpressed in atherosclerotic coronary arteries (535), and that LPS from *Escherichia coli* (*E. coli*) localized in human plaques and may contribute to atherosclerosis progression via TLR4-mediated mechanisms (54).

In addition to immune system activation, LPS can promote oxidation. LPS administration to isolated human saphenous vein preparations resulted in increased ROS production and increased IL-8 and CCL2 expression in a TLR4-dependent manner (417). Indeed, LPS endotoxemia has been associated with increased LDL oxidation via NOX2 activation (538). Besides TLR4, other mechanisms have been suggested for LPS-mediated effects on atherosclerosis. Indeed, a meta-analysis of patients with impaired TLR4 signaling due to Asp299Gly mutation showed no reduction in atherosclerotic risk (595), indicating that other mechanisms could be implicated.

A growing amount of evidence also supports the role of TMAO in atherosclerosis (287, 460, 611). Plasma concentrations of TMAO, *p*-cresyl sulfate, *p*-cresyl glucuronide, and phenylacetylglutamine were increased in patients with high plaque burden attending vascular prevention clinic (36). Experiments using ApoE^{-/-} mice models demonstrated that adding choline to diet resulted in increased plaque burden and increased foam cell formation (243).

Coagulation modulation

Following the identification of TMAO as a risk factor of CVD, studies involving mouse models showed proatherogenic properties of dietary supplementation of TMAO and its precursors (153, 243, 550). One prospective cohort study involving 4007 patients undergoing elective coronary angiography showed that high TMAO levels were associated with increased risk of incident major adverse cardi thrombotic events (MI, stroke, or death) after adjustment for traditional risk factors and in a dose-dependent manner (503). Furthermore, intraperitoneal TMAO administration resulted in increased thrombosis following carotid injury in mice, and platelets from healthy low TMAO donors subjected to exogenous TMAO (100 μ M) showed increased activation and collagen binding following ADP or thrombin exposure (611). This was mediated by TMAO potentiation of Ca²⁺ release following ADP stimulation (611).

The prothrombotic effects of TMAO are dependent on gut microbiome as administering choline to germ-free mice eliminated TMA production and decreased thrombosis following carotid injury. Moreover, transfer of cecal matter to low TMAO mice resulted in increased thrombosis (611), and suppression of FMO3 expression by antisense oligonucleotides in mice resulted in reduced platelet activation (610). Similar results were subsequently reported by transfer of human commensal colonies to mice (473) and by administering choline to healthy subjects in a small human prospective study (612). TMAO may also be implicated in inducing tissue factor (TF) expression as observed in *in vitro* cultured endothelial cells (72). Additionally, germ-free mice showed

reduced plasma levels of von Willebrand factor (VWF) and reduced thrombus growth after carotid artery injury (196).

LPS is another important modulator of thrombosis (537), and endotoxemia is associated with increased CV risk (213, 238, 269). Infusion of LPS into mice resulted in increased thrombus formation and platelet activation (56). Higher LPS and soluble P-selectin levels were found in plasma of patients with ST elevation MI (STEMI) compared to patients with stable angina or healthy controls (56). This was further demonstrated by directly detecting LPS in thrombotic lesion samples from MI patients (56, 346, 437). Interestingly, a genome-wide association study (GWAS) performed by Leskelä et al. found that endotoxemia was associated with significant genetic variants [single-nucleotide polymorphism (SNPs) in five independent loci], which were mainly located at genes affecting the contact activation of coagulation cascade and lipoprotein metabolism (269). LPS-induced activation of thrombosis is mediated by binding to TLR (TLR2, TLR9, and TLR4) on multiple target cells. Exposure of platelets to LPS resulted in increased potentiation of platelet activity *in vitro* (360), while endothelial cell exposure to LPS resulted in increased expression of TF, thrombin-activatable fibrinolysis inhibitor, plasminogen activator inhibitor 1, von Willebrand factor, and factor VIII (55, 430, 598), all in a TLR4-dependent manner (55, 416). TLR4 is also expressed on leukocytes, and exposure of leukocytes to LPS results in overexpression of cathepsin G, which is an important protein for leukocyte platelet activation (346, 437). In addition to lymphocytes, neutrophils are also important in plaque inflammation and instability (454). Interestingly, LPS can stimulate neutrophils to release reactive oxygen species (ROS) and extrude neutrophil extracellular traps (NETs) in a TLR4-dependent manner (231).

Hypertension

BP regulation has been demonstrated to be affected by gut microbiota (5, 198, 315, 343, 407). Fecal transfer experiments from hypertensive mice resulted in increased BP in nonhypertensive mice recipients (114, 222, 280, 322), and this was also demonstrated when using human fecal microbiota transplantation (FMT) (280). Recently, changes in the gut microbiota resulting from intermittent fasting were shown to reduce BP in hypertensive metabolic syndrome patients (306).

Association studies found that *Clostridium* spp., *Prevotella* spp., and Lachnospiraceae were linked to hypertension (107, 280). Additionally, high salt intake was shown to reduce the population of *Lactobacillus murinus*, and addition of this species prevented hypertension in mice models (280). These species were also associated with systolic BP variability, nighttime dipping, and morning BP surge, suggesting a dynamic role of the gut microbiota and metabolites in the regulation of BP variability (107).

Investigating dietary effects on BP revealed that fiber content was essential for BP reduction (123). Further studies revealed that morning BP surge was negatively correlated

with plasma levels of SCFA ($r = -0.31$, $P = 0.02$) (107), and that butyrate reduced diastolic BP (427). These effects were found to be mediated by Gpr41 and Olfr78 receptors. As mentioned before, binding of the SCFA propionate to Gpr41 results in BP drop in Olfr78^{-/-} mice, while propionate binding to Olfr78 results in increased BP in Gpr41^{-/-} mice (390). The overall reduction in BP following SCFA administration is thus suggested to result from reduced cardiac output coupled with reduced vascular resistance (394, 395).

TMAO also plays a role in BP modulation as increased TMAO levels were found to be associated with increased BP (202, 296). Indeed, a meta-analysis comprising 10,293 cases and 18,854 total participants found significant association between TMAO levels and hypertension risk (HR 1.39; 95% CI: 1.22–1.57; $P = 3.47 \times 10^{-7}$) with a dose response of 7% increased risk of hypertension per 1 $\mu\text{mol/liter}$ increase in TMAO levels (HR 1.07; 95% CI: 1.03–1.11; $P = 6.49 \times 10^{-4}$) (275). TMAO may act on BP by inducing protein kinase r-like endoplasmic reticulum kinase (PERK), resulting in phospholipase c β 3 (PLC β 3) activation and angiotensin-II-mediated vasoconstriction (139, 202).

Additional factors such as increasing plasma bile acid levels by cholic acid, oleanolic acid supplementation, or even intermittent fasting resulted in reduced systolic BP in hypertensive rats (306), indicating the existence of a complex interaction between multiple factors.

Inflammation and immune activation

The link between increased immune activation and CVD is well established (2, 141, 263) and is mediated by multiple cell types, cytokines, and other factors (119). CVD is associated with increased CRP levels, and inhibition of IL1 β by canakinumab (418) or administration of colchicine (356, 506) resulted in reduced CVD risk. Gut microbiota can affect host inflammatory state either directly by activating gut resident immune cells or indirectly by systemic activation through absorbable soluble metabolites.

The gut barrier is the first line of defense against invading pathogens and their metabolites. It is composed of a mucus layer containing multiple antimicrobial proteins (190, 208) and gut epithelial cells connected by tight junctions. The gut innate immune system may be considered as the next line of defense and is composed of resident dendritic cells, neutrophils, and macrophages. The gut adaptive immune cells include mainly $\gamma\delta$ -T, CD4, CD8, TH17, and Treg cells (47). Gut microbiota intricately affects gut barrier integrity and both the innate and adaptive immune response. Indeed, the mucus layer can be altered by western diet (484) and probiotics consumption. Furthermore, epithelial cells utilize SCFA both as nutrients and for proper tight junction function (382, 603). SCFA effects the innate immune response by binding to FFAR2 (GPR43) on neutrophils and macrophages (264, 358), facilitating chemotaxis (488, 510, 536). Additionally, butyrate was shown to inhibit histone deacetylase 3 (HDAC3), resulting in increased monocyte to macrophage

differentiation (451). SCFA effects the adaptive immune response by reducing Th1 and Th17 levels, while upregulating Treg levels resulting in overall inflammation reduction (310). Indeed, butyrate can induce Foxp3+ Treg cell differentiation by binding to FFAR2 and HDAC inhibition (171, 475). The pTreg population seems to have bidirectional relationship with the gut microbiota as recent studies in mice showed that IL10+/IL17+ gut pTreg were upregulated by *Methylococcus capsulatus* lysate. In turn, this increase in pTreg population resulted in microbiome compositional shifts similar to changes seen in low-fat diet fed mice (546). SCFA can also induce B-cell activation and differentiation (439). However, the overall effect of SCFA seems to help uphold the gut barrier and reduce inflammation.

In addition to its pro-atherosclerotic and -thrombotic activity, TMAO also promotes immune activation by inducing TNF- α and IL-1 β , while reducing IL-10 levels (456). Furthermore, TMAO can activate NLRP3 inflammasome (38, 67, 489), resulting in NF- κ B activation and vascular inflammation (67, 456, 599). Secondary bile acid binding to FXR and TGR5 receptors can dampen innate immunity activation by inhibiting monocyte-derived dendritic cell activation and NF- κ B signaling (187). Furthermore, secondary bile acids were shown to increase IL10-dependent M2 macrophage polarization (32). The adaptive immune response is also modulated by secondary bile acids modulating ROR γ +Treg cells (479) and suppressing TH1 and Th17 cells (167, 372).

Conditions resulting in endotoxemia accelerate an inflammatory response (297, 558). LPS activates the innate response by binding TLR4 on neutrophils and macrophages (332). In addition, LPS can prime and activate NLRP3 inflammasome in immune cells, blood vessel endothelial cells, and cardiomyocytes (110). LPS activates NLRP3 in one of two pathways, the canonical pathway through TLR binding and NF- κ B activation, and the noncanonical pathway utilizing Caspase 4/5, both pathways culminating in cleavage and activation of IL1 β and IL18 (110, 225). Taken together, it seems that immune modulation by microbiota and their metabolites plays an important role in CVD development.

Heart-liver axis

Nonalcoholic fatty liver disease (NAFLD)

NAFLD and CVD share multiple risk factors. Understanding the link between these two conditions is important to allow efficient screening and primary prevention strategies. CV mortality was shown to increase in NAFLD (9, 45, 483), and a meta-analysis of 25,837 patients has shown that NAFLD confers an increased risk for CV events (RR 1.77, 95% CI: 1.26–2.48; $P < 0.001$) (162), and consistent results were reported by other studies (312, 471, 507, 566). NAFLD patients are at higher risk of atherosclerosis and CAD (118, 228) and arrhythmias (16, 45, 508), especially AF (216, 371, 509), but also prolonged QT (191) and increased prevalence

of premature ventricular complexes (PVCs) and nonsustained ventricular arrhythmia (VT) (314) as well as HF (311, 313, 329, 371) with greater prevalence of HF with preserved ejection fraction (HFpEF) compared to HFrEF (329, 386). However, contradicting data exist with some meta-analyses not detecting a significantly increased CV risk associated with NAFLD (566), and a prospective follow-up study of NAFLD patients did not detect a significant association between liver fibrosis severity and the risk of MACE (443). Animal model studies have shown the importance of gut microbiota in NAFLD. FMT from NAFLD predisposed mice to wild-type mice resulted in worsening steatosis (182). FMT from mice with steatosis to germ-free mice resulted in increased expression of genes involved in lipid metabolism (265), and FMT from vegan mice resulted in lower hepatic inflammation (557). Assessing bacterial populations in weight-matched mice showed an increase in Lachnospiraceae bacterium 609 and *Barnesiella intestinihominis* (265). FMT experiments were also instrumental in showing the role of human microbiota in NASH as transfer of fecal matter to mice resulted in increased steatosis and inflammation (74, 186). Further experiments were able to detect specific bacterial fingerprints of the various degrees of hepatic damage. NAFLD patients demonstrated increased Enterobacteriaceae (463) and decreased Rikenellaceae (98) and Ruminococcaceae (463, 544), specifically, an increase in *Escherichia* (186), *Dorea* (98), and *Peptoniphilus* (98) and a decrease in *Anaerosporebacter* (544), *Coprococcus* (544), *Eubacterium* (186), *Faecalibacterium* (608), and *Prevotella* (40, 463) in fecal matter were reported. Progression of hepatic fibrosis was associated with decreased *Bacteroides*, *Ruminococcus*, and *Shigella* genera (40, 463) as well as with increased *Prevotella* genus (301). Interestingly, oral microbiota has been found to be associated with liver damage, including changes in the abundance of *Prevotella* (70), *Veillonella* (544), and *Streptococcus* (58).

The bidirectional relationship between the gut and its metabolites and the liver is termed the “gut-liver axis,” which results from the transport of gut-derived metabolites from the portal vein to the liver and the ability of the liver to modify metabolites and influence the gut microbiota by bile and antibody secretion to the intestine (516). An important aspect of this axis is the balance between the ability of the liver to neutralize toxic metabolites and the amount of toxins passing through the intestinal barrier (516). Interestingly, microbial biomarkers shown to affect CVD are also of importance in NAFLD (18, 516). TMAO levels are correlated to hepatic damage in NAFLD (71, 268, 302, 478) and are proposed to affect the liver metabolically by modulating glucose metabolism and promoting local inflammation through NLRP3 and NF- κ B activation (599). Mice models have demonstrated that the addition of SCFA to mice fed with reduced choline diets improved steatosis and inflammation (102). Similarly, endotoxin levels are elevated in NAFLD (50), and inhibition of TLR4 resulted in improved steatosis (124). Modulation of the gut barrier

by bile acids combined with their effect on glucose and lipid metabolism also plays an important role in NAFLD progression (516).

Alcoholic liver injury

Excessive alcohol use and its deleterious effects on liver function may result in changes to gut microbiota and gut barrier integrity (78, 375, 474). Interestingly, these changes result in increased levels of metabolites also seen in NAFLD, such as LPS (404) and TMA (181). Indeed, alcohol-induced liver damage has been, at least partly, attributed to activation of TLR4, NLRP3, and NF- κ B pathways, similar to other conditions resulting in dysbiosis and gut barrier damage (239).

Given these similarities, it is tempting to consider that at least part of the cardiac damage resulting from chronic alcohol consumption is mediated by gut dysbiosis. However, this notion needs further investigation as a recent study showed that in spite of increased TMA levels detected during alcohol use, TMAO levels were not significantly increased presumably due to reduced FMO3 levels in the liver (181).

The fact that several metabolites are involved in both CVD and liver injury combined with the presence of shared comorbidities indicates that gut microbiota play an important role in these two conditions and may represent a pivotal axis in the metabolic syndrome state.

Diabetes mellitus (DM)

The role of the gut microbiota in both type 1 and 2 DM has been extensively studied (99, 477) and is beyond the scope of this review. Briefly, FMT experiments demonstrated that insulin resistance could be transmitted in mice models (527, 596), and that dietary intake affected the gut microbiota composition and postprandial glucose levels (592). Improved insulin sensitivity was associated with increased abundance of *E. hallii* (299, 526), and type 2 DM was associated with reduced butyrate-producing bacteria, including *Roseburia intestinalis* and *F. prausnitzii*, and increased populations of *Lactobacillus gasseri*, *Streptococcus mutans*, Clostridiales, *Desulfovibrio*, and Proteobacteria (220, 261, 547). In type 1 DM, patients had increased *A. shahii* and *R. hominis* (468).

Mechanistically, the microbiota-driven effect on DM may be mediated in part by TMAO as increased levels of TMAO have been associated with increased risk of DM (504). TMAO can directly bind to protein kinase R-like endoplasmic reticulum kinase (PERK) and induce the transcription factor FoxO1, a key driver of metabolic disease (68). Additional evidence suggests that the gut microbiota-mediated effect on bile acids may also play an important role in the pathogenesis of DM (75, 157).

Chronic kidney disease (CKD)

CKD is a major independent risk factor for CVD (414), and CV events are the leading cause of death in end-stage

renal disease (ESRD) patients (207). It is associated with sudden cardiac death, atherosclerotic CVD, arrhythmias, HF, ventricular hypertrophy, and aortic stenosis (207). The increased risk of CVD seen in CKD patients independently of other risk factors triggered the quest to identify cardiotoxic metabolites that are normally eliminated by the kidneys. Impaired renal function results in increased levels of uremic toxins, including TMAO (333). This is supported by the lack of CVD risk reduction seen in patients undergoing hemodialysis, which does not remove most uremic toxins, and the reduced CVD risk seen following renal transplantation (39, 412), which regains the capability of removing uremic toxins (291, 292, 393). CKD was associated with decreased Lactobacillaceae, Prevotellaceae (532), Clostridia, and *Bacillus* population (13) and increased Enterobacteriaceae, Lachnospiraceae, Ruminococcaceae, and *Enterococci* populations (438) as well as an overall increase in species demonstrating urease activity (559). These changes result in increased translocation of bacteria and bacterial toxins across the gut barrier (13). FMT from CKD patients to antibiotic-treated rats resulted in increased TMAO production (569). In addition, CKD patients demonstrated lower levels of SCFA (321). Interestingly, recent large-scale trials have demonstrated that part of the CV beneficial effects of SGLT2 inhibitors among non-DM patients is mediated by the ability of SGLT2 inhibitors to increase carbohydrate levels in the colon, allowing saccharolytic fermentation and reduced *p*-cresol sulfate levels (331).

Obesity

Obesity is an independent risk factor for multiple CVD conditions, including CAD, HF, and arrhythmias (399). Furthermore, obesity adversely affects other metabolic CV risk factors, such as dyslipidemia, hypertension, and DM (399), collectively termed the cardiometabolic syndrome. Gut microbiota have been extensively implicated in obesity (409), but the full breadth of evidence is beyond the scope of this review. Multiple animal studies have demonstrated transmissibility of adiposity (524), and in human studies, infusing intestinal microbiota from lean donors to human recipients with metabolic syndrome improved insulin resistance and increased levels of butyrate-producing intestinal microbiota (541). Furthermore, specific strains, such as *Akkermansia*, *Faecalibacterium*, *Oscillibacter*, and *Alistipes*, were implicated in increased weight, while other species, such as *A. shahii*, were found to be depleted in obesity (515). The interaction between obesity and CVD is well demonstrated by CVD risk reduction seen in patients following bariatric surgery (131), which may be, at least partially, mediated by alterations in the composition of the gut microbiota (496). Interestingly, studies involving only lifestyle changes have demonstrated that CVD benefits only when weight loss was greater than 10% of the baseline body weight (The Look AHEAD Research Group (154)). Consequently, studies investigating the changes in gut microbiota

among obese individuals after partial weight reduction are of interest.

Sex differences

Sex-dependent differences in CVD risk are well documented (482). These differences were initially attributed to divergent CV risk factors, such as smoking and sex hormone exposure (12, 87). However, in the past few years, differences in microbiota populations have emerged as a possible contributor to sex-specific CVD patterns. Animal models have demonstrated that female mice have lower Bacteroidetes population (590), and that removing the ovaries (oophorectomy) from rats resulted in increased gut microbial diversity (84). Reports in humans have shown that females have higher Firmicutes/Bacteroidetes (F/B) ratio (111, 282, 341, 442). However, overweight males have lower Bacteroidetes levels compared to overweight females, suggesting a more complex interaction (173). Specifically, women were found to have increased Proteobacteria, *Veillonella*, and *Blautia* species (173, 282, 448), and further changes in gut microbiota were detected during pregnancy (149). The differences in microbial populations may partly result from differences in dietary habits as increased yogurt consumption by women resulted in increased *Lactobacillus casei*, while men showed reduced *Lactobacillus sakei*, Enterobacteriaceae, and *Staphylococcus* (493).

The use of animal models has allowed the identification of sex dimorphic differences in specific pathways. For instance, TMAO levels were shown to be higher in female rats (319), which may be due to higher expression levels of FMO3 than their male counterparts (28). Indeed, castration results in increased FMO3 expression with a concomitant elevation in TMAO levels (28), and this effect could be reversed by administration of testosterone. Similarly, oophorectomy resulted in reduced FMO3 expression in female mice, and this was reversed by administration of estrogen (28). Hypothetically, increased TMAO levels may result in increased platelet activation, which could be beneficial in reducing bleeding risk during pregnancy and delivery (539). Studies in humans have also demonstrated that female liver samples have higher expression levels of FMO1/3 (28), and that female platelets contain more TLR mRNA when compared to males (251). However, genome-wide association studies (GWAS) did not detect sex-specific variants in *FMO3* gene (174, 553), and regression analysis did not detect any difference in all-cause mortality between male and female subjects in a large TMAO meta-analysis (445). It is worth noting that the lack of sex-dependent differences in TMAO levels may be a result of studies having relatively low female representation and increased postmenopausal female representation (555). As microbiota-based interventions are developed to mitigate CVD risk, a better understanding of sex dimorphic traits is needed to provide tailored solutions for women.

Specific Cardiovascular Effects

As delineated above, gut microbiota are implicated in multiple processes known to promote cardiac disease. In this section, we describe the evidence supporting a direct involvement of the gut microbiota and their associated metabolites in cardiac-specific disorders. Table 1 summarizes the main clinical studies demonstrating the implication of gut microbiota in CVD.

Coronary artery disease

Cohort studies of CAD patients showed lower levels of Bacteroidetes, *Roseburia*, *Eubacterium*, and *A. shahii* populations with increased Firmicutes populations (85, 130, 205, 440, 583, 609). Antibiotic-treated mice undergoing MI showed significantly higher mortality and reduced myeloid cell infiltration in the infarcted zone (555). Additionally, there was reduced presence of CX3CR1-positive monocytes in the peri-infarct zone, suggesting impaired repair capacity. These changes were associated with reduced *Lactobacillus* population and mediated by reduced SCFA levels. Supplementing antibiotic-treated mice with *Lactobacillus* probiotics before MI or administration of SCFA negated the effects of antibiotics (555). Similarly, MI size was increased when cecal microbiota were transferred from obese leptin-deficient mice to control C57Bl/6j mice, and this was associated with reduced SCFA (25). Interestingly, treatment of rats with oral vancomycin resulted in reduced infarct size, which was also seen by addition of either *Lactobacillus plantarum* 299v (259) or aromatic amino acids, suggesting potential beneficial as well as harmful interactions with gut microbiota.

TMAO has also been shown to be associated with CVD progression, MACE, and thrombotic events (165, 287, 397, 445, 459, 497, 549). In one study involving 4007 patients admitted for elective coronary angiography, TMAO levels were a significant predictor of nonfatal MI or stroke after 3 years of follow-up (HR 2.13; CI 1.48–3.05; $P < 0.001$) (503, 552). This was further confirmed with inpatients presenting with STEMI (287, 464, 497), non-ST elevation MI (NSTEMI), and acute coronary syndrome (ACS) (542). When examining coronary atherosclerosis, TMAO was found to be associated with increased atherosclerotic burden as determined by angiography, Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (459), and OCT analysis and showed that it was also associated with increased coronary artery calcification (279).

LPS endotoxemia is another avenue by which the gut microbiota influences coronary disease. Large cohort studies ($n = 7927$, with a 10-year follow-up) showed significant correlation between LPS and risk of CV events (405). Similar data were obtained by studying 3781 patients with type 1 DM patients and over a 15-year follow-up (472). LPS is also increased in patients with ACS (143, 607), and LPS levels were shown to be higher in ACS compared to chronic CAD patients (56). Data from early-phase MI patients showed

Table 1 Main Clinical Studies Demonstrating the Implication of Gut Microbiota in Cardiovascular Disease

Study by	Year	Research topic	Subjects	Method	Outcome
<i>Oral microbiota</i>					
Pussinen et al. (405)	2007	Association between oral pathogen and LPS to CVD incidence	6051 stratified random population survey of 24 to 64-year-old individuals	<i>A. actinomycetemcomitans</i> and <i>P. gingivalis</i> IgA, IgG, and endotoxin levels 10-year follow-up	Exposure to periodontal pathogens or endotoxin induces systemic inflammation, leading to increased risk for CVD
Koren et al. (248)	2011	The correlation between bacteria from the oral cavity and gut, and atherosclerosis	15 CVD, 15 healthy controls	16S rRNA and confirmed by qPCR	The combined abundances of <i>Veillonella</i> and <i>Streptococcus</i> in atherosclerotic plaques correlated with their abundance in the oral cavity
Hyvärinen et al. (192)	2012	The association between angiographically verified CAD and salivary levels of four major periodontal pathogens	179 CAD, 166 ACS, 119 healthy controls	qPCR	High salivary levels of <i>A. actinomycetemcomitans</i> were associated with increased risk for CAD
Fak et al. (125)	2015	The association between oral microbiota and asymptomatic/symptomatic atherosclerosis patients	27 symptomatic patients, 35 asymptomatic patients, 30 healthy controls	16S rRNA	Symptomatic patients had higher relative abundance of <i>Anaeroglobus</i> than the control group. <i>Parvimonas</i> associated positively with uCRP and <i>Capnocytophaga</i> , <i>Catonella</i> , and <i>Lactobacillus</i> associated with blood lipid markers.
<i>Gut microbiota</i>					
Dinakaran et al. (106)	2014	To study the circulating human microbiome in CVD patients and healthy subjects	80 CVD patients, 40 healthy controls	16S rRNA and metagenomic sequencing (shotgun)	Increased: Proteobacteria, Actinobacteria, Protonibacterium phages, Pseudomonas phages, Rhizobium phages, lymphocystis virus, and Torque Teno viruses
Asnicar et al. (21)	2021	Identification of bacterial association with diet and cardiometabolic score	1097 healthy adults	Shotgun metagenomic sequencing	Association with composite cardiometabolic score Favorable: <i>Firmicutes</i> CAG95 <i>F. prausnitzii</i> , <i>P. copri</i> , <i>E. eligens</i> and <i>H. parainfluenzae</i> , <i>Roseburia</i> CAG182, <i>Oscillibacter</i> sp. 57_20, <i>Firmicutes</i> bacterium CAG170, <i>Oscillibacter</i> sp. PC13, <i>Clostridium</i> sp. CAG167, and <i>Roseburia</i> CAG182 Detrimental: <i>C. spiroforme</i> , <i>C. bolleae</i> CAG59, <i>C. bolleae</i> , <i>Clostridium</i> CAG58, <i>C. symbiosum</i> , <i>C. innocuum</i> , <i>C. leptum</i> , <i>R. gnavus</i> , and <i>F. plautii</i>
Salosensaari et al. (435)	2021	Association of microbiome with mortality risk	7055 representative cohort (FINRISK population surveys)	Shotgun sequencing with 14.8-year follow-up	Enterobacteriaceae family major association to mortality; however, CV mortality was increased but not significant (HR 1.12 CI: 0.99–1.27, FDR 0.11)

Coronary artery disease	Karlsson et al. (219)	2012	The role of the gut metagenome in the development of symptomatic atherosclerosis	12 symptomatic, 13 healthy controls	Gut metagenome	<i>Collinsella</i> was enriched in patients, while <i>Eubacterium</i> and <i>Roseburia</i> were enriched in healthy subjects
	Yin et al. (583)	2015	The association between gut microbial diversity and blood TMAO levels in large artery atherosclerotic stroke or transient ischemic attack patients	141 stroke/TIA patients, 97 asymptomatic controls	16S rRNA	Increase in CVD: Enterobacteriaceae, Proteobacteria, and <i>Escherichia/Shigella</i> Decrease in CVD: Bacteroidetes, Bacteroidales, Bacteroidaceae, and Bacteroides
	Emoto et al. (117)	2016	The association between gut microbiota and coronary artery disease	39 CAD patients, 30 control subjects with risk factors, 50 healthy subjects	T-RFLP	Increase in CAD: Firmicutes/bacteroidetes ratio, Lactobacillales decrease in CAD: <i>Bacteroides</i> + <i>Prevotella</i>
	Feng et al. (130)	2016	The association between diet, the gut microbiome, and CAD	59 CAD patients, 43 healthy controls	Gut metagenome	Increase in CAD: <i>Streptococcus</i> sp. M334 and M143, <i>Clostridium</i> sp. HGF2
	Kelly et al. (226)	2016	To explore the relation between composition of the gut microbiome and lifetime CVD risk profile	55 high CVD risk, 57 low CVD risk	16S rRNA	Increased: <i>Prevotella</i> and <i>Tyzzerella</i> Decreased: <i>Alloprevotella</i> , <i>Catenibacterium</i>
	Sanchez-Alcoholado et al. (440)	2017	The role of gut microbiota on cardiometabolic parameters and immunity in CAD patients with and without DM2	16 DM2, 16 non-DM2	16S rRNA	Increased: Enterobacteriaceae, <i>Streptococcus</i> , and <i>Desulfovibrio</i> 30 Decreased: <i>Faecalibacterium prausnitzii</i> and <i>Bacteroides fragilis</i>
	Cui et al. (85)	2017	Identify bacteria species associated with CAD	29 CHD in-hospital patients 35 healthy controls	16S rRNA	Bacteroidetes (56.12%) was lower and that of phylum Firmicutes was higher (37.06%) in CHD patients than those in the controls (60.92% and 32.06%, $P < 0.05$)
	Jie et al. (205)	2017	The gut microbiome's composition and function in relation to atherosclerotic cardiovascular disease	218 atherosclerotic patients 187 healthy controls	Shotgun sequencing	Increased abundance of Enterobacteriaceae and <i>Streptococcus</i> spp. in patients
	Zhu et al. (609)	2018	To characterize the dysbiosis signatures of gut microbiota in coronary artery disease	70 patients with CAD 98 controls	16S rRNA	Increased: <i>Escherichia-Shigella</i> , <i>Lactobacillus</i> , <i>Enterococcus</i> , and <i>Streptococcus</i> . Decreased: <i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Eubacterium</i> , and <i>Subdoligranulum</i>
	(continued overleaf)					

Table 1 (Continued)

Study by	Year	Research topic	Subjects	Method	Outcome
STEMI					
Li et al. (287)	2017	TMAO correlation to MACE during 30, 6 month and 7-year follow-up	530 patients presenting with chest pain to ED 1683 all patients undergoing coronary angiography for ACS	Blood samples at presentation, 4, 8, and 16 h later	TMAO levels predict both short- and long-term risks of cardiovascular events in patients with chest pain
Zhou et al. (607)	2018	Association between LPS and circulating blood bacteria with CVD incidence in STEMI patients	50 stable CAD, 100 STEMI, 49 healthy controls	16S rDNA, LPS from blood samples at admission, 3 years follow-up	Increased post-STEMI gut <i>Lactobacillus</i> , <i>Bacteroides</i> , and <i>Streptococcus</i> translocation with concomitant increase of LPS
Sheng et al. (464)	2019	Relation between TMAO levels and the coronary atherosclerotic burden in patients with STEMI	335 patients with STEMI 53 healthy controls	TMAO blood levels and SYNTAX score	Significant colocalization between high TMAO levels and high SYNTAX score
Tan et al. (497)	2019	Relation between TMAO levels and plaque rupture in patients with STEMI	STEMI patients undergoing coronary angiography with preintervention OCT: 77 plaque rupture, 69 plaque erosion, 53 healthy controls	TMAO blood sample at presentation	TMAO independently correlated with plaque rupture in patients with STEMI
NSTEMI/ACS					
Tang et al. (503)	2013	TMAO correlation to MACE during 3-year follow-up	4007 adults undergoing elective diagnostic coronary angiography	Fasting blood samples	TMAO was associated with an increased risk of a major adverse cardiovascular events
Wang et al. (552)	2014	TMAO metabolites correlation to MACE during 3-year follow-up	3903 adults undergoing elective diagnostic coronary angiography	Fasting blood samples	Higher plasma choline and betaine levels were associated with an increased risk of MACE
Waleed et al. (542)	2021	Association between TMAO and coronary atherosclerotic burden in NSTEMI	73 new NSTEMI 35 healthy controls	- Atherosclerotic burden assessed by SYNTAX and GENSINI during coronary angiography - Fasting blood TMAO levels prior to angiography	Median plasma TMAO levels were significantly higher in the NSTEMI versus healthy controls

Heart failure

Pasini et al. (376)	2016	Difference in gut microbiota between mild HF (NYHA II-III) compared to severe (NYHA III-IV)	30 mild HF (LVEF 39 ± 1.4) versus 30 severe HF (LVEF 35.0 ± 1.2) 20 healthy controls	48 h of incubation on selective agar	Decompensated HF patients had higher levels of endotoxemia compared to compensated HF or healthy controls
Kamo et al. (214)	2017	The link between HF gut microbiota and aging	12 HF patients <60 years 10 HF patients ≤60	16S rRNA	In older patients with HF, Bacteroidetes were reduced, Proteobacteria were increased, and <i>Lactobacillus</i> was enriched
Luedde et al. (303)	2017	Identification of gut microbiota changes in HF	20 HF rEF (LVEF 22.3 ± 2.85) 20 controls	16S rRNA	Significant decrease of <i>Blautia</i> , <i>Collinsella</i> , uncl. <i>Erysipelotrichaceae</i> , and uncl. <i>Ruminococcaceae</i> in HF compared to controls
Hayashi et al. (176)	2018	Gut microbiome and plasma microbiome-related metabolites in patients with decompensated and compensated heart failure	22 HF patients 11 controls	16S rRNA	An enriched phylum of Actinobacteria in HF patients compared with control subjects. At the genus level, <i>Bifidobacterium</i> was abundant, while <i>Megamonas</i> was depleted in HF patients.
Cui et al. (86)	2018	Identification of differences in bacterial composition and metabolite pathways between CHF patients and healthy controls	53 CHF (median LVEF 29.7 ± 6.5) 41 controls	Paired-end sequencing of bacterial DNA	86 genera were differentially enriched in CHF including <i>Ruminococcus</i> , <i>Acinetobacter</i> , and <i>Veillonella</i> , while <i>Alisipies</i> , <i>Faecalibacterium</i> , and <i>Oscillibacter</i> were decreased
Kummen et al. (254)	2018	Identification of HF bacterial signature	84 HF 266 controls	16S rRNA	HF had decreased microbial richness. HF had increased abundance of Prevotellaceae <i>Prevotella</i> , Lachnospiraceae <i>Hungatella</i> , and Acidaminococcaceae <i>Succiniclasticum</i> and decreased Lachnospiraceae <i>Anaerostipes</i> , L. <i>Blautia</i> , L. <i>Coprococcus</i> , L. <i>Fusicatenibacter</i> , L. Lachnospiraceae, L. <i>Pseudobutyrvibrio</i> , L. <i>Eubacterium hallii</i> , L. <i>Faecalibacterium</i> , Ruminococcaceae <i>Faecalibacterium</i> , and Bifidobacteriaceae <i>Bifidobacterium</i>
LPS in heart failure					
Niebauer et al. (357)	1999	Increased endotoxemia in HF	20 HF patients with recent edema 20 HF patients without edema 14 healthy controls	Blood sample analysis	Increased endotoxemia in decompensated HF compared to stable and healthy controls
Peschel et al. (385)	2003	Assessment of endotoxemia and inflammation in acute HF	17 acute HF 21 stable HF 9 healthy controls	Blood sample analysis	Increased endotoxemia, IL6, and TNFα in acute HF. Highest levels of endotoxin detected in hepatic vein compared to left ventricle

(continued overleaf)

Table 1 (Continued)

Study by	Year	Research topic	Subjects	Method	Outcome
<i>TMAO in HFpEF</i>					
Tang et al. (502)	2014	TMAO correlation to risk of death in stable HF patients	720 stable HF patients 300 healthy controls	Blood samples and 5-year mortality	Increased TMAO correlates to increased risk of death at 5 years
Trøseid et al. (523)	2015	Evaluate the prognostic value of TMAO in HF	155 HF patients 33 healthy controls 100 stable CAD without HF	Blood samples, left- and right-sided cardiac characterization, and echocardiography. Follow-up for 5.2-year mortality	TMAO, choline, and betaine are elevated in HF patients compared to control. TMAO was correlated to increased 5.2-year mortality
Israr et al. (195)	2022	TMAO metabolites as gut dysfunction surrogate markers predict outcome in HF	1783 worsening or new HF (LVEF <40%) patients	Blood samples and 3-year follow-up	Acetyl-L-carnitine, γ -butyrobetaine, L-carnitine, TMAO, and TFF-3 were associated with increased HF hospitalization or all-cause mortality at 3 years
<i>TMAO in HFpEF</i>					
Tang et al. (505)	2015	TMAO correlation to HF type and mortality risk	112 stable HF (LVEF $26 \pm 6\%$ with 40% diastolic dysfunction stage III)	Blood samples and echocardiographic evaluation and 5-year mortality	High TMAO levels correlated with diastolic dysfunction but not LVEF. Increased TMAO correlated with 5-year mortality
Schuett et al. (449)	2017	Asses the association of TMAO with CV death risk in HFpEF vs HFpEF	428 HFpEF 395 HFpEF From total 2490 patients referred for coronary angiography	Blood samples and 9.7-year follow-up	TMAO levels were higher in all HF patients compared to non-HF patients. TMAO was associated with risk of CV death in HFpEF but NOT HFpEF patients
Guo et al. (161)	2020	TMAO correlation to HFpEF	228 HFpEF (LVEF > 50%) 96 healthy controls	Blood samples	HFpEF patients had higher TMAO than controls
Kinugasa et al. (236)	2021	TMAO correlation to HFpEF outcome	146 acute decompensated HFpEF (LVEF > 50%)	Blood samples and registry follow-up	High TMAO levels correlated with increased risk of cardiac death or HF hospitalization
<i>TMAO in acute heart failure</i>					
Suzuki et al. (491)	2016	TMAO correlation to outcome in acute HF patients	972 acute HF patients	Blood samples and 1-year follow-up	Lower TMAO levels were correlated with improved in-hospital death. Increased TMAO correlated worse 1-year outcome
Kamo et al. (214)	2017	Changes in gut bacterial composition in HF patients and the effect of age on HF microbiota	22 Hospitalized acute decompensated HF 12 healthy controls	16S rRNA	<i>Eubacterium rectale</i> and <i>Dorea longicatena</i> were significantly reduced in samples from HF patients compared to HC subjects
Israr et al. (194)	2021	Association of TMAO with outcome in acute HF	806 acute HF	Blood samples and 1 year follow-up	TMAO and its metabolites were associated with death and HF at 30 days and 1 year

Table 1 (Continued)

Study by	Year	Research topic	Subjects	Method	Outcome
<i>Atrial fibrillation</i>					
Pastori et al. (378)	2017	Effect of Mediterranean diet on LPS association with MACE in AF patients	912 non-valvular AF patients on Vit. K antagonists	Blood samples and median follow-up of 3.3 years	Increased LPS levels correlated with MACE. Mediterranean diet was correlated with reduced LPS levels
Svingen et al. (494)	2018	Assess the correlation between TMAO and increased risk of AF	412 AF of 3797 suspected angina patients (WECAC) 484 AF of 3143 community cohort (HUSK)	Blood samples and follow-up 7.3 years WECAC, 10.8 HUSK	TMAO increases the risk of AF in a dose-dependent manner
Yamagami et al. (571)	2018	Association of indoxyl sulfate with AF recurrence after PVI	125 nonvalvular AF patients scheduled for RFCA	Blood samples and up to 1-year follow-up	High indoxyl sulfate at baseline correlated with lower 1-year AF-free survival
Nguyen et al. (354)	2021	Investigate the association of TMAO between peroxisomal and persistent AF	78 rhythm controlled mixed persistent and peroxisomal AF patients with max 3 years AF	Blood samples	TMAO levels were significantly higher in patients with persistent AF, as compared to those with paroxysmal AF

Abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; ACS, acute coronary syndrome; AF, atrial fibrillation; AS/SS, asymptomatic/symptomatic atherosclerosis; TIA, transient ischemic attack; HTN, hypertension; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HF-rEF, heart failure with reduced ejection fraction; CHD, congestive heart disease; DM2, type-2 diabetes mellitus; ED, emergency department; MACE, major adverse cardiovascular events; SYNTAX score, synergy between percutaneous coronary intervention (PCI) with taxus and coronary artery bypass surgery (CABG) score; 16S rRNA, 16S ribosomal RNA; qPCR, realtime polymerase chain reaction; T-RFLP, terminal restriction fragment-length polymorphism; TMAO, trimethylamine N-oxide; LPS, lipopolysaccharides.

that increased LPS levels were associated with an increased incidence of MACE after a 3-year follow-up (607). Interestingly, these patients also showed increased gut permeability as detected by D-lactate levels. Furthermore, small intestinal bacterial overgrowth (SIBO) was more pronounced among patients with established CAD (177). Collectively, these findings demonstrate an important interaction between the gut microbiota and myocardial ischemia (144, 607).

Heart failure

HF is a complex and multifactorial syndrome affecting multiple organs with gradual functional decline resulting from reduced effective perfusion and edema. These processes do not skip the intestinal wall (135), thereby resulting in physical, ischemic, and bacterial composition disturbances (141, 398, 499). These changes allow unwanted bacterial species to thrive, thus increasing toxic metabolites production, which are easily absorbed through the permeable intestinal barrier. Hence, a vicious cycle, also termed “gut-heart axis,” is created in which alterations in the composition and function of the gut microbiota (dysbiosis) and increased intestinal wall permeability result in increased toxin and metabolite absorbance by the host leading to HF propagation (491, 492, 523, 601). It was suggested that part of the mechanisms driving this “gut-heart axis” is gut hypoperfusion in combination with increased renin/aldosterone levels and subsequent increased epithelial sodium/hydrogen exchanger 3 activity, resulting in intestinal pH changes and bacterial population variations.

Cohort studies have demonstrated that HF patients have reduced populations of Coriobacteriaceae, Erysipelotrichaceae, Ruminococcaceae (family level), *Blautia* (genus level), *Eubacterium rectale*, *Dorea longicatena*, *Eubacterium hallii*, *Faecalibacterium*, and Bifidobacteriaceae and increased populations of *Ruminococcus gnavus*, *Prevotella*, *Hungatella*, and *Succinellasticum* (86, 176, 214, 254, 303, 318, 376). In addition to these changes in bacterial composition, an increase in the overall growth and mucosal biofilm formation was also observed in HF (441). Indeed, a recent study found that SIBO was detected in 45% of HF patients, and that SIBO was associated with higher New York Heart Association (NYHA) class. Additionally, SIBO was an independent risk factor for hospitalization for HF or CV death (HR 2.13, 95% CI: 1.26–3.58; $P < 0.001$) (480). HF patients also demonstrated increased populations of pathogenic microbiota such as *Campylobacter*, *Shigella*, *Yersinia*, and *Candida* spp. (376). However, the effect of these pathogenic gut microbiota on chronic HF progression besides the acute HF decompensation setting is unclear and needs further evaluation.

Mechanistically, it is hypothesized that gut microbiota's effect on HF could be mediated by increased inflammatory state (422), endotoxemia (357), or/and toxic metabolites. Evidence suggests that LPS plays a role in HF as higher levels of LPS were detected in decompensated HF patients

compared to stable controls (385). This may result from increased edema and reduced barrier integrity seen in decompensated HF patients (195, 436, 491), thus enhancing LPS leakage into the circulation and driving inflammation (441). Indeed, studies have shown that the levels of trefoil factor-3 (TFF-3), a biomarker of gut dysfunction (1), were elevated in HF and are an independent predictive factor for the occurrence of CV events in HFpEF patients (115).

The effect of TMAO on HF pathogenesis was demonstrated in animal models following transverse aortic constriction (TAC). Mice fed with TMAO- or choline-rich diet showed a significant increase in fibrosis area, BNP levels, and heart mass and reduced systolic function compared to chow-fed mice (366). Plasma TMAO was significantly higher in rats following TAC compared to sham-operated rats when both were fed the same diet, and TMAO was directly involved in cardiac hypertrophy and fibrosis through Smad3 signaling (290). In humans, multiple studies reported that elevated TMAO levels were associated with worse outcome in HFpEF (57, 284, 491, 505, 523, 601). Even among patients admitted for coronary angiography, TMAO levels were found to be significantly higher in HF patients (449). Reanalysis of 1783 HF patients from the BIOlogy Study to Tailored Treatment in Chronic HF (BIOSAT-CHF) (540) found that metabolites of the carnitine-TMAO pathway (acetyl-L-carnitine, γ -butyrobetaine, L-carnitine, and TMAO) were associated with an increased risk of the composite outcome of HF hospitalization, or all-cause mortality after 3 years of follow-up with greater number of elevated markers was associated with higher NYHA class, higher levels of natriuretic peptides, and worse outcomes. Interestingly, choline *per se* was not associated with HF outcomes in this study, indicating that the carnitine-TMAO metabolites (acetyl-carnitine, trimethyllysine, octanoyl-carnitine, and palmitoyl-carnitine) but not the choline pathway metabolites are more clinically important and contribute to HF severity (195).

The role of TMAO in HF was further investigated in the context of HFpEF with mixed results. Initial data comparing 428 HFpEF and 395 HFpEF patients showed no association between TMAO levels and the overall or CV death in HFpEF patients (449). However, recent data from a cohort study of 146 patients with HF and left ventricular ejection fraction (LVEF) $>50\%$ showed that higher TMAO levels were associated with an increased risk of hospitalization and a higher risk of the composite outcome of cardiac death or HF hospitalization (236). It should be noted that TMAO levels were very high in this study (average of 20.4). However, similar results were obtained in other two small studies (161, 194) with median TMAO levels of 12.65 $\mu\text{g/liter}$ and 6.6 $\mu\text{mol/liter}$, respectively.

While the significance of TMAO in chronic compensated HF was extensively studied in large populations, little is known about its significance in the setting of acute HF. One study has reported that higher levels of TMAO at the time of hospitalization were associated with increased in-hospital mortality and a composite of death or HF rehospitalization

among patients admitted to the hospital due to decompensated HF (491). Further data is needed to determine whether this observation reflects direct implication of TMAO in HF progression, or whether TMAO is a marker of poor prognosis. Elevated TMAO levels at discharge were also associated with an increased risk of postdischarge cardiac events (including CV death and hospitalization for HF) in patients with HFpEF, and the prognostic significance of TMAO was more enhanced in patients with malnutrition (236). Interestingly, TMAO levels differ substantially according to the country of origin, with highest levels seen in Japanese HF patients (median: 9.9 $\mu\text{mol/liter}$) followed by Caucasian (5.9 $\mu\text{mol/liter}$) and South Asian patients (4.5 $\mu\text{mol/liter}$) (581). However, these differences do not reflect the local prevalence of HF as Japan has only 0.8% HF compared to 1.4% to 4% in Europe and 2.4% to 3.6% in northern America (155). This discrepancy may reflect more complex dietary and genetic differences, as a polymorphism in the *FMO3* gene, for example, was shown to confer increased risk of CKD (356, 421, 554).

Atrial fibrillation

Atrial fibrillation affects millions, with prevalence increasing by age reaching up to 17% at the age of 80 (602). Interestingly, gut microbiota also shows age-related changes, specifically a decrease in *Bacteroides*, *Bifidobacteria*, and *Lactobacilli* and an increase in *Enterobacteriaceae*, *Clostridium perfringens*, and *Clostridium difficile* (362). Zhang et al. showed differences in β diversity and reduced age-related Firmicutes-to-Bacteroidetes ratio (F/B ratio) in an animal model comparing young versus old rats. Specifically, they detected an increase in *Spirochaete* and a decrease in *Verrucomicrobia* in aging rats (184, 602). In addition, FMT from AF-prone old rats resulted in increased susceptibility to burst pacing-induced AF in young rats (602).

Multiple studies showed that increased inflammatory state enhances AF development (197). This may be partly mediated by LPS as higher levels of LPS have been associated with adverse effects in AF patients (378). Moreover, age-related alterations in the composition of gut microbiota have been shown to affect LPS levels by increasing endothelial permeability. Using an FMT rat model from old to young rats resulted in shorter colonic villi and increased oral fluorescein isothiocyanate (FITC)-dextran uptake, indicating that aged microbiota transplantation induced gut barrier dysfunction (602).

As mentioned above, LPS may contribute to AF development by promoting atrial inflammation (602). Indeed, old to young FMT resulted in elevated levels of toll-like receptor 4 (TLR4), NOD-like receptor protein (NLRP)-3 inflammasome, pro-caspase-1, activated caspase-1, NF- κ B, and IL-1 β in rat atrial samples. This was followed by increased atrial fibrosis and overexpression of TGF- β 1 and α -SMA (602). Furthermore, LPS infusion in animal models resulted in reduced duration of both atrial action potential and effective refractory period. This is likely due to reduced L-type

Ca²⁺ current accompanied by increased I_{kr} and I_{ks} currents (127, 490). These effects, together with the evidence of increased Ca²⁺ release from the sarcoplasmic reticulum (due to increased Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) and Na⁺/Ca²⁺-exchanger activity) (127), were hypothesized to be responsible for delay after polarization and reentry mechanisms (180, 260, 295, 351, 455, 579). LPS-mediated effects on rat atria were mitigated by concomitant administration of LPS from *Rhodobacter sphaeroides* (LPS-RS) (a TLR4 antagonist) and MCC950 (an inflammasome inhibitor) (602).

Furthermore, NLRP-3 inflammasome signaling has been shown to be activated in cardiomyocytes obtained from patients with AF compared to cardiomyocytes from non-AF individuals (579). This study has established a pathophysiological role of NLRP-3 inflammasome signaling in cardiomyocytes and provided a mechanistic link mediated by apoptosis-associated speck-like protein (ASC), pro-caspase-1, and activated caspase-1, thereby raising the potential of NLRP-3 inhibition as a novel target for AF therapy. Bile acids may also be implicated in AF pathogenesis. Chenodeoxycholic acid activates NLRP-3 and includes atrial fibrosis (152, 403). Bile acids have been shown to increase Na⁺/Ca²⁺ exchanger (NCX) currents resulting in faster after depolarizations and induced arrhythmias in human atrial preparations (410). However, other studies reported that FXR activation inhibits IL1 β in rat aortic specimens (142), hence indicating that further data is needed to elucidate the role of bile acids in AF development.

Analysis of 6940 patients from the Western Norway Coronary Angiography Cohort (WECAC) and Hordaland Health Study (HUSK) community-based Norwegian cohorts identified a significantly increased risk for developing AF in association with increased TMAO levels (HR 1.16, 95% CI: 1.05–1.28 and HR 1.10, 95% CI: 1.004–1.19 per 1 SD increase in log-transformed plasma TMAO levels, respectively) (494). Furthermore, TMAO levels were increased in persistent AF patients compared to paroxysmal AF in a small study (354). The PRMID (PREvencion con DIeta MEDiterranea) trial involving 509 AF incidents and 618 matched controls showed that although baseline choline and betaine levels were significantly associated with AF risk (OR 1.85, 95% CI: 1.30–2.63 and OR 1.57, 95% CI: 1.09–2.24, respectively), the TMAO and L-carnitine levels were not significantly associated with AF (373). TMAO may exert its proarrhythmic effects by enhancing inflammation and fibrosis. Increased TMAO levels in DM rats have been associated with elevated atrial levels of IL-1 β , IL-6, and TNF- α in addition to the downregulation of connexin 40 and maldistribution of connexin 43. These changes may, at least partially, explain the higher AF inducibility seen in DM rats (203).

Uremic toxins can increase oxidative stress (17), and increased indoxyl sulfate results in increased pulmonary vein and atrial arrhythmias while depressing sinoatrial node activity (69). Furthermore, indoxyl sulfate was independently

associated with increased risk of AF recurrence (571). A more recent study of 138 AF patients undergoing catheter ablation demonstrated that ablation resulted in reduced indoxyl sulfate only in non-CKD patients despite improvement in estimated glomerular filtration rate in the CKD group, suggesting a more complex relationship (245).

Microbiota Interventions Affecting Cardiovascular Risk

Diet

Several studies have provided evidence that different diets confer different CV risks. This could be linked to the important interplay between the effect of dietary changes on gut microbiota and the implication of gut microbiota in CVD pathogenesis and progression (122). The relative ease and safety of changing diet make this an attractive option for both primary and secondary prevention approaches (3).

According to the data from the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study including 237,036 men and 179,068 women with nearly 78,000 deaths (22,228 due to CVD) after 16 years of follow-up, increased dietary plant protein intake was significantly associated with reduced overall mortality in both sexes (HR 0.95, 95% CI: 0.94–0.97 per 1 SD for men and HR 0.95, 95% CI: 0.93–0.96 for women). The reduction in mortality was mainly due to CVD (189). This observation was confirmed by a large meta-analysis of 715,128 participants with 3.5 to 32 years of follow-up showing that plant-based protein intake conferred a significantly lower risk of CVD mortality (pooled HR 0.88; CI: 0.80–0.96, $P = 0.001$) (347) and other large prospective studies (29, 400). An increased risk was observed in animal-based protein intake mainly attributed to red and processed meat (3). Consumption of fish, poultry, and eggs was not found to be associated with increased CVD risk (113, 229, 408, 548, 605, 606).

Mediterranean diet (based on vegetables, nuts, fruits, and olive oil with reduced consumption of red meats and refined grains) (556) reduced CVD in the PREDIMED trial (530) and a recent large meta-analysis encompassing 35,548 individuals (217), and it is the basis for the dietary recommendation for prevention of CVD (529). Not surprisingly, adhering to Mediterranean diet results in differences in gut microbiota composition compared to the western diets (145, 172, 325). Recently, Wang et al. (546) performed deep shotgun metagenomic sequencing of fecal samples from 307 male participants in the Health Professionals Follow-up Study (HPFS) demonstrating that the protective associations of the Mediterranean diet with CVD risk vary depending on the microbial composition, and these associations were significantly stronger in participants with decreased abundance of *Prevotella copri*. The importance of *P. copri* as a favorable microbial signature of CV health was further confirmed in the PREDICT 1 study (21). Interestingly, intestinal *P. copri*

strains were shown to be variable in the western population, and the diversity of *P. copri* strains in gut microbiome was found to be affected by diet (92, 512). Western, animal-based, diet was found to be associated with increased populations of bile-tolerant microbiota, including *Alistipes*, *Bilophila*, and *Bacteroides* and reduced numbers of *Roseburia*, *Eubacterium rectale*, and *Ruminococcus bromii* (90). *Roseburia intestinalis* was demonstrated to confer protection from atherosclerosis in ApoE^{−/−} mice by producing butyrate from plant polysaccharides (211).

The negative CV consequences of increased red meat consumption could be mediated by an increase in TMAO production (243). A crossover randomized control trial (RCT) involving 113 healthy volunteers showed that dietary red meat consumption increased plasma and urine TMAO levels through increased microbial TMA/TMAO production from carnitine but not choline. Discontinuation of dietary meat resulted in reduced plasma TMAO within 4 weeks (549). This is consistent with small differences seen in choline content between dietary red and white meat and a high endogenous choline pool (558). Supplementation of L-carnitine to mice resulted in increased TMAO levels (242), and consistent results were obtained in humans (136, 330). The ability to transform carnitine to TMAO was found to be greater in omnivores, which may be attributed to differences in the composition of gut microbiota. Direct oral carnitine challenge resulted in higher levels of TMAO in omnivores compared to vegetarians after 24 h of consumption (567). Inversely, reducing red meat consumption or high intake of phosphatidylcholine and carnitine (precursors of TMAO) resulted in reduced TMAO levels (93, 549). Thus, achieving lower TMAO levels by adhering to healthy diet may be beneficial in reducing CVD risk (178). Interestingly, Jun et al. recently identified microbial taxa that modify associations of dietary precursors with TMAO concentrations and cardiometabolic risk markers. Specifically, the authors found that TMAO levels were elevated after red meat consumption mainly in individuals harboring *A. shahii* and *E. bifforme* (277). Therefore, it is tempting to hypothesize that in addition to Mediterranean diet and reduced red meat consumption, manipulation of specific bacterial populations may modulate cardiometabolic health and contribute to further reduction in CVD.

TMAO is also present at high concentrations in fish with concentrations increasing in deep sea fish (573). High TMAO concentrations seem to act as a protein stabilizer and were even suggested to act as antifreeze (521), allowing continued function in the cold and high pressure and osmolarity conditions of the deep sea (574). Consumption of fish directly increases TMAO levels without the need for intermediate metabolites (76, 447). Despite higher TMAO levels, extensive data showed that increased fish consumption actually lowered CVD risk (258, 339). However, when controlling for identical protein intake from milk or soy, mice fed with fish-based protein had greater levels of atherosclerosis (582), suggesting that consumption of deep-sea fish may be less beneficial.

In spite of these encouraging results, the efficacy of diet in reducing TMAO levels is still controversial. The Prevention with Mediterranean Diet trial (PREDIMED), a prospective cohort study, showed that levels of choline metabolites (including TMAO) were associated with increased CVD risk. However, after 1 year of Mediterranean diet, no significant reduction of CVD risk was detected in this study (158). Similar results were reported in smaller studies (121, 388, 470). There may be several explanations for the lack of major effects seen in these studies, including adherence to diet, which could be challenging and affected by many cultural and noncultural factors, need for validation studies, and difficulties in adjusting for important interventions, such as antibiotic use (560). This may be the reason why significant dietary changes are needed to achieve significant effects (126).

TMAO is not the only mediator of dietary changes affecting the risk of CVD. High-fat diet resulted in increased plasma LPS levels in mice (345). In participants with metabolic syndrome, LPS was reduced by a 75-day fiber-rich diet (160), with similar results reported by consuming Mediterranean diet (378). Besides specific diets, recent data show that fasting reduces Clostridial Firmicutes, *F. prausnitzii*, *Eubacterium rectale*, and *Coprococcus* comes population (105, 306). These changes affect the ability to maintain a controlled BP using the DASH diet, which may be mediated by changes in the immune system (306). This data is supported by observational studies showing increased SCFA-producing bacteria in healthy individuals fasting for Ramadan (370). Additionally, physical activity may favorably affect gut microbiota as interventional studies have shown a decreased abundance of *A. shahii* in physically active pre-DM men (299).

Probiotics

The notion of manipulating gut microbiota to affect the host has been extensively studied (426, 486) with conflicting results. However, as certain bacteria are associated with increased CVD risk, attempts were made to manipulate specific bacterial populations. Studies in animal models showed that the addition of *Akkermansia muciniphila* to ApoE^{-/-} mice was associated with reduced atherosclerotic burden (278), and introducing *Lactobacillus rhamnosus* GR-1 resulted in improved left ventricular function in an MI rodent model (137). Manipulation of LPS-producing bacteria, such as administration of live *A. muciniphila* to ApoE^{-/-} mice, resulted in reduced gut permeability, lower LPS, and attenuated atherosclerosis (278). Interestingly, not all LPS are identical as gavage of *Bacteroides (vulgatus and dorei)*, which produce penta- and tetraacylated lipid A of LPS, resulting in reduced endotoxemia and atherosclerosis in mice, while gavage of *E. coli*, which produces hexa-acylated lipid A, did not (586).

Initial small human RCT trials showed that addition of *L. plantarum* (DSM 9843) to atherosclerotic patients resulted in increased microbial diversity with concomitant changes in SCFA levels (218). Similarly, addition of *Saccharomyces*

boulardii resulted in improved LVEF in HF patients (80), and addition of pasteurized *A. muciniphila* for 3 months resulted in reduced LPS levels (103).

Despite these encouraging results, real-life advantages have been elusive. A recent meta-analysis of 10 small RCT studies encompassing 342 patients (168 intervention and 174 control) showed no effect of probiotics (varied bacteria, single or mixed preparations) on TMAO levels (327). This is further supported by lack of improvement in LVEF in a recent RCT of 151 HFrEF patients treated with rifaximin or *Saccharomyces boulardii* for 3 months (23).

This disappointing effect may be a result of limited bacterial survivability and colonization capabilities (90, 230) or difficulty in recognizing the most effective microbial population for manipulation. Additionally, safety needs to be addressed before widespread recommendations can be made due to reports of adverse effects in immunocompromised persons (132, 381).

Prebiotics

A more indirect approach to changing microbiota populations is by manipulating specific nutrient intake to favor production of beneficiary metabolites or promote specific populations (335, 587). One strategy tested the possibility of reducing BP by enhancing SCFA production utilizing increasing dietary fibers (315, 343). This effect seems to depend on microbiota as minocycline-treated rats showed reduced BP with a concomitant increase in acetate- and butyrate-producing species (577). Furthermore, addition of fibers or acetate to mice diet could negate BP increase after mineralocorticoid administration (316). Similarly, lack of dietary fibers resulted in increased BP after Angiotensin II stimulation, which was negated by addition of acetate, butyrate, and propionate in mice (222). In both studies, BP reduction by SCFA resulted in reduced cardiac fibrosis and left ventricular hypertrophy, indicating that the effect might be of clinical significance (222, 316). Indeed, dietary manipulation of SCFA levels seems to be reflected in human trials where increased intake of fruits, vegetables, or high-fiber diet has been demonstrated to be an effective means for reducing BP (315).

As mentioned above, dietary restriction of red meat and processed food resulted in reduced TMAO levels and improved cardiometabolic outcome. However, carnitine is a popular dietary supplement used to increase muscle mass. An interesting recent Phase 2 prospective double-blind RCT of 157 participants evaluated the effect of carnitine supplementation over 6 months. Surprisingly, no difference in carotid total plaque volume between groups was found. However, the carnitine arm did show significantly increased carotid stenosis (9.3% difference $P=0.02$) with increased total cholesterol and LDL-C levels (210). Longer surveillance, greater number of participants, and more diverse age groups may be needed to reveal the deleterious CV effects of increased carnitine consumption.

In conclusion, manipulating specific dietary components is easier to adhere to than overhauling complete diets. As more metabolites involved in cardiometabolic damage are discovered, manipulating dietary intake will be a more feasible option to try to mitigate CVD progression.

Antibiotics

Antibiotics have acute widespread effects on gut microbiota, which result in alteration in the composition of the bacterial communities such as those seen in *Clostridioides difficile* infection. However, this effect is not merely limited to acute use but can also have profound long-standing effects. There is growing evidence suggesting that antibiotic use in early life can increase the risk for DM (300, 600), obesity (520), and various immune responses (431), presumably through changing the microbial diversity (359). Experiments in mice showed that antibiotic use resulted in reduced endothelial dysfunction and decreased plasma TMAO levels (41). However, this beneficial effect was not translated into a noticeable clinical benefit as large prospective RCTs examining azithromycin, roxithromycin, clarithromycin, and gatifloxacin for secondary prevention following ACS did not show significant benefits (15). Thus, besides a potential harm from creating bacterial resistance, there is a lack of apparent CV effects, thereby making antibiotics a poor therapeutic choice.

Interestingly, antibiotic resistance was recently shown to be associated with meat consumption due to increasing veterinary use of antibiotics (66). Further studies are needed to examine whether changes in the microbial composition observed with high meat consumption are due to antibiotic resistance acquisition by specific bacterial populations.

Specific inhibitors

Bacterial-directed inhibitors

In contrast to antibiotics and food supplementation, which affect multiple species, the identification of TMAO synthesis pathways allowed the development and testing of specific inhibitors. Initial studies with 1,3 dimethylbutanol (DMB), a nonlethal choline analog that inhibits the transformation of choline to TMA, showed promising results with reduced foam cell formation and reduced aortic atherosclerosis development in ApoE^{-/-} mice (551). Importantly, DMB was found to be present in extra virgin olive oil and may be part of the link between Mediterranean diet and reduced CVD risk (551). Next, targeted design and screening enabled Roberts and colleagues to develop the highly potent irreversible and noncompetitive cutC/D inhibitors, fluoromethylcholine and iodomethylcholine. Administering these inhibitors to mice resulted in marked reduction in TMAO levels and reduction in platelet activation and carotid thrombus propagation (420). Iodomethylcholine was also demonstrated to improve ventricular remodeling and cardiac function in a transverse

aortic constriction HF model (365). In addition, recent data showed that these inhibitors positively affect obesity and glucose utilization, suggesting broader metabolic effects (450). The overall cardiometabolic improvement is suggested to result not only from reducing TMA levels but also from Iodomethylcholine-induced increase in bacterial choline uptake, leading to choline sequestration from TMA-mediated pathways (420). Betaine aldehyde is another cutC inhibitor capable of inhibiting choline-dependent bacterial growth in anaerobic conditions (367). Despite these promising findings, to date, there are no clinical trials utilizing these drugs, and the ability of other bacterial pathways to produce TMA such as cutA/b and gbuA may require a broader approach. Indeed, a recent report in which shotgun metagenomic sequencing was used to analyze 22 HF patients found cutA/B rather than cutC/D to be positively correlated with plasma TMAO levels (116).

Host-directed inhibitors

As we unveil the molecular pathways involved in microbiota-mediated cardiac damage, it may be possible to target host-driven process for therapeutic purposes. FMO3 inhibition may result in reduced TMAO levels; however, better understanding is needed as higher levels of FMO3 seen in woman did not correlate with differences in all-cause mortality (445). It will also be interesting to further investigate whether FMO3 inhibition in both males and females has any cardiac specific effects. SCFA acts on multiple molecular targets; SCFA induced FFAR2/3 activation, resulting in increased GLP-1 levels. The cardioprotective roles of GLP-1 have been demonstrated in coronary artery disease and AF (37, 528). It is tempting to consider that direct FFAR 2/3 activation could induce the same cardioprotective effect as direct GLP-1 agonists with fewer side effects. Additionally, animal model studies have demonstrated that SCFA receptor Gpr41 knockout results in hypertension (350). Inhibition of Gpr41 may present as a novel antihypertensive strategy; however, the complex interplay with Olfr78 needs further study.

TLR inhibition may represent another possible intervention avenue. TLR inhibition was shown to improve CV damage in multiple animal models of hypertrophy (221), HF (364), and diabetes (589). To date, the only clinically relevant drugs with some TLR inhibitory effect are chloroquine (and its derivatives), statins, and angiotensin II receptor blockers (ARBs) (138). While statins and ARBs are cardioprotective, chloroquine has cardiotoxic effects, suggesting that there is more than one pathway involved in its activity. TLR signal transduction inhibition is another possible therapeutic option with multiple drugs targeting multiple steps converging on NF-κB inhibition (411). PI3K inhibitors, such as copanlisib, duvelisib, idelalisib, and alpelisib, are in clinical use but are known to have multiple CV adverse effects ranging from prolonged QT to pro-arrhythmogenic effects and HF. Other targets in this pathway include CRM1 inhibition of p65

NF- κ B subunit-facilitated nuclear export such as Selinexor. Inhibitors of histone acetylation and DNA methylation, both important for NF- κ B transcription activation, may also be of potential use. However, drugs such as azacitidine, decitabine, vorinostat, and romidepsin have multiple cardiotoxic side effects, while others such as belinostat, panobinostat, and tucidinostat seem safer. NLRP3 inflammasome inhibition poses intriguing possibilities with early studies being performed on models of diabetes, NASH (79), and cardiac damage (349, 465); however, no drug has yet matured for clinical use.

Cardiac FXR activation by secondary bile acids may inhibit IL1 β secretion (142, 289), making treatment with chenodeoxycholic acid (CDCA). Several reports have demonstrated favorable clinical effects of SGLT2 inhibitors on gut microbiota in diabetes and diabetic kidney disease (101, 562). Since SGLT2 inhibitors are now a well-established beneficial therapy for HF, it is of great interest to further investigate how changes to microbiota exerted by SGLT2 inhibition contribute to the overall cardioprotective effects. Furthermore, it is of interest to investigate whether microbiota alterations may play a role in the magnitude of response to SGLT2 inhibitors and the resultant impact on clinical outcomes in patients with HFrEF or HFpEF.

Fecal transplantation

FMT efficacy in the treatment of recurrent *Clostridioides difficile* infection has been demonstrated in multiple studies (100, 215), and it is currently a valid treatment option for refractory cases. Furthermore, FMT has shown promising results in the treatment of other conditions, including IBD (81) and even cancer (91). FMT was demonstrated to modify CVD risk factors, such as weight gain (6), insulin sensitivity, DM (541), and lipid metabolism (353). Autologous FMT from banked samples obtained during Mediterranean diet consumption was shown to prevent weight gain after diet discontinuation (419).

Patient-acceptable delivery along with organism survivability of FMT samples (413) makes preparations and delivery methods (freeze-dried, colonic enema, and nasogastric tube) of great importance. Indeed, evidence suggests that approximately half of the fecal microbiota is not viable, and some species do not survive when using current collection methods (27). In addition to these technical issues, multiple factors may also influence FMT efficacy, including recipient/donor baseline microbiota (247), concomitant medication use, diet, and even blood group compatibility between the donor and the recipient (170).

These inherent and technical problems have resulted in variable results when testing the effect of FMT on modifying CV risk. For example, FMT from lean donors showed no effect on glucose metabolism in obese participants despite evident engraftment (588). Similarly, no effect on TMAO levels was detected following FMT from vegan subjects (476). The lack of effect is further compounded by safety issues,

such as infection (53) and transfer of antibiotic resistant strains (97), which need to be resolved before considering FMT as a reasonable treatment option.

Drug metabolism

CVD prevalence increases with age and the appearance of other comorbidities and risk factors, such as hyperlipidemia, hypertension, and DM, requiring the use of multiple medications. Recent studies have demonstrated that there are multiple interactions between oral medications and the microbiome (200, 534). These interactions can change the effective drug levels and the microbiome populations and metabolism. Indeed, large-scale *in vitro* screening of common drugs showed that several compounds had antibiotic-like properties affecting at least one microbial population (305). However, recent data using deep shotgun metagenomic sequencing of fecal samples found that only a small portion of the drugs tested (~1%) had a significant effect on bacterial variability (546), warranting further investigation.

Statins are a major drug for primary and secondary CVD prevention. The importance of statin-microbiota interactions was demonstrated by showing that statin-driven effects vary among individuals based on the composition of the gut microbiota (604). Furthermore, statins were shown to reduce TMAO levels (51, 232, 233, 255, 276, 361, 604) in an independent manner (328) and improved gut barrier function by upregulating several intestinal adhesion molecules (533, 597) and reducing the risk of endotoxemia (417).

Recently, a retrospective analysis of 1196 patient pairs (propensity matched) undergoing coronary intervention demonstrated that statins were associated with reduced TMAO levels, and that statin discontinuation resulted in return to baseline TMAO levels (275). This was prospectively tested in two small studies showing similar effects (275). It is tempting to hypothesize that at least part of the reduction in CV risk attributed to statins may be mediated by modulation of gut microbiota and reduced TMAO levels. However, further research is needed to unravel the complexity of the statin-microbiota interaction and its effect on the CV system.

There is evidence of an interaction between the gut microbiota and other commonly used drugs for the treatment and prevention of CVD. Increased levels of amlodipine were detected in ampicillin-treated rats (584), and enalapril was shown to increase intestinal barrier properties by increasing gut perfusion (383). Furthermore, metformin was shown to have antibiotic-like properties affecting the gut bacterial populations in FMT to germ-free mice experiments (561). Deeper understanding of drug-microbiota interactions may provide more insights into the interpatient variations seen in clinical practice and allow a tailored administration of specific drugs based on the composition of gut microbiota of each individual in a personalized medicine approach.

Conclusions

Human commensal microbiota is essential for multiple host processes ranging from metabolite processing to neurological well-being. As perturbation of host conditions results in substantial changes in microbiota, the realization of codependence resulted in the meta-organism concept. The complex bidirectional interaction between the CV system and microbiota seems to play an important role in almost all aspects of cardiac pathology. However, as gut microbiota is also intimately related to many CV risk factors, such as DM, hypertension, CKD, and NAFLD, great care has been given to isolate the direct effect of microbiota on CV system. Multiple large studies have demonstrated that adjusted CV risk increases in association with alterations in the composition of unique gut bacterial communities, and animal models are complementing our knowledge with controlled mechanistic pathways. Several metabolites have been implicated in CVD pathogenesis and disease progression as well as in several cardiometabolic risk factors. Since advances in sequencing metagenomics and proteomics are utilized to enrich our knowledge of host-microbiota interactions, it will be exciting to reveal novel metabolites and further elucidate the role of different microbial species colonizing the intestine in the development of CVD. There is a hope that broader understanding of gut microbiota and its derived metabolites will allow for tailored interventions to mitigate the residual CVD burden.

Authors Disclosures

The authors have no conflicts of interest to disclose.

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