Review Article

The emerging role of gut microbiota in cardiovascular diseases

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A B S T R A C T

There is mounting evidence which suggests the involvement of gut microbiota dysbiosis in the pathogenesis of various cardiovascular diseases (CVD) and associated risk states such as hypertension, type 2 diabetes, obesity and dyslipidaemia, atherosclerosis, heart failure and atrial fibrillation. The current review comprehensively summarizes the various pathogenetic mechanisms of dysbiosis in these conditions and discusses the key therapeutic implications. Further deeper understanding of the pathogenetic links between CVD and gut microbiota dysbiosis can aid in the development of novel microbiota-based targets for the management of CVDs.

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1. Introduction

The term 'microbiome' was coined by Lederberg and McCray to denote the group of commensal, symbiotic and pathogenic microorganisms (including majorly bacteria along with viruses, protozoa and fungi) dwelling in the human body.[1,2] According to the latest estimates, the ratio of the number of bacterial to human cells in humans has been revised from 10:1 to 1:1.[3] The majority of these microorganisms are found in the human gastrointestinal tract and are collectively termed as 'gut microbiota'; their collective genome is referred to as 'gut microbiome'.[2]

The adult gut microbiota is diverse and majorly consists of bacteria from the phyla, *Bacteroidetes and Firmicutes*. The other less abundant phyla include *Proteobacteria, Verrucomicrobia, Actinobacteria*, and *Fusobacteria*.[4,5] The composition of the gut microbiota undergoes transition from an infant to adult and may vary depending on several factors and health conditions,[5,6] which may in turn, have wide therapeutic implications. The advent of newer molecular techniques such as deep 16 S rRNA sequencing has enabled microbial profiling and research into the role of the gut microbiota in human health and diseases.[5]

Several factors may potentially alter the gut microbial composition. The type of diet one follow significantly impacts the gut microbiota. While vegetarian diet has been found to be associated with healthy and diverse gut microbiota, non-vegetarian diet has been found to be associated with a decrease in overall gut microbiota and beneficial species. The mode of delivery also impacts the gut microbiota. While newborns delivered vaginally have vaginal microbiota in excess, new-borns delivered via caesarean derive microbiota from the skin. The primary microbiota after birth evolves over time and stabilizes at the age of three. Physiological changes and weakened immune activity affect the microbial composition among the elderly. Besides, exposure to pathogens and usage of antibiotics can alter he gut microbial composition.[7]

The evolving significance of gut microbiota in maintaining homeostasis and pathogenesis of several diseases is being increasingly appreciated. Gut microbiota has been found to play a vital role in the maturation and regulation of the immune system of the host.[8] It also modulates various metabolic pathways in the host.[9,10] Further, alterations in the composition of gut microbiota have been found to have significant implications on cardiovascular health in humans.[11,12]

Cardiovascular disease (CVD) is the leading cause of mortality, worldwide.[13] Therefore, considering the accumulating evidence on

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the role of gut microbiota alterations in the pathogenesis of CVD, we conducted this narrative review, to evaluate and discuss the plausible association between gut microbiota and CVD and its risk factors and the therapeutic implications that this association may have, on the cardiovascular health in humans. The role of gut microbiota and derived uremic toxins in chronic kidney disease (CKD) has also been described in brief as some of the risk factors for CVD and CKD overlap.

2. Gut microbiota and risk factors for cardiovascular diseases

Perturbations in the composition of the gut microbiota is known as 'dysbiosis'. Dysbiosis has been linked to the development and progression of various CVDs. Gut microbiota plays a central role in regulating the energy harvesting process and metabolism in the host. Alteration in microbial flora along with changes in the gut-microbiota-derived metabolites have been shown to have a significant association with several risk factors for CVD.

2.1. Gut microbiota and diabetes mellitus

2.1.1. Pathogenetic mechanisms
Type 2 diabetes mellitus (T2DM) is one the major risk factors for CVD. Recent observational studies and systematic reviews on the association between gut microbiota and T2DM have revealed key differences in the gut microbiota composition between people with T2DM and healthy controls. While, the genera of bacteria with a protective role in glucose metabolism and T2DM such as *Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia* and *Roseburia* were found to be less abundant in individuals with T2DM; the phylum, *Firmicutes* and the genera of bacteria such as *Ruminococcus, Fusobacterium,* and *Blautia* were positively associated with T2DM.[14,15] The genus, *Lactobacillus* with the highest number of operational taxonomic units (OTUs) in the human gut, was noted to be diverse with discrepant distribution patterns.[14]

Multiple mechanisms have been postulated to explain the potential association between altered gut microbiota and T2DM, including modulation of inflammation, gut permeability, glucose and fatty acid metabolism and insulin sensitivity. Specific species of bacteria from the genera, *Roseburia, Bacteroides, Lactobacillus* and *Akkermansia* have been observed to induce the production of anti-inflammatory cytokines and chemokines such as interleukin (IL)-10 and 22, and transforming growth factor (TGF)-β; and inhibit pro-inflammatory cytokines and chemokines such as IL-1β, monocyte chemoattractant protein-1, intercellular adhesion molecule-1, IL-8, IL-16, IL-17, CD36, nuclear factor-kappa B (NK-κB), interferon (IFN)-γ and C-reactive protein, thus preventing inflammation and enhancing insulin sensitivity. On the contrary, bacteria from the genera, *Ruminococcus, Fusobacterium* have been reported to augment the production of cytokines that promote inflammation.[13] Further, reduction in gut permeability by enhancing the expression of tight junction genes through activation of adenosine monophosphate kinase (AMPK) by *Bacteroides* and *Akkermansia* genera has been noted to prevent metabolic endotoxemia.[14] Another important mechanism is through modulation of fatty acid oxidation in adipose tissue. The action of gut microbiota on indigestible carbohydrates and proteins results in the formation of short-chain fatty acids (SCFAs) which regulate several endocrine pathways in humans. They trigger the release of postprandial plasma peptide YY (PYY) and glucagon-like-peptide-1 (GLP-1) by binding to G protein-coupled receptors, GPR41 and GPR43.[14,16,17] Additionally, SCFAs also activate AMPK, a key regulator of metabolic homeostasis.[18] Further, SCFAs and SCFA-producing bacteria such as *Bacteroides, Akkermansia* and *Lactobacillus* have been found to increase fatty acid oxidation and energy expenditure and reduce the synthesis of fatty

acids, which may help improve T2DM.[14] Of note, the gut-microbiota of T2DM patients has been found to have lower levels of bacteria that produce SCFAs such as butyrate.[19]

2.1.2. Therapeutic implications
Evolving understanding of the role of gut microbiota dysbiosis in the pathogenesis of T2DM has paved way to various strategies for ameliorating this disease. Recently, faecal microbial transplantation (FMT) in experimental models has been shown to be effective in alleviating the symptoms associated with T2DM. This treatment strategy lowered the insulin resistance and markers of inflammation in the pancreas and reversed the increased serum insulin level associated with T2DM. There was an improvement in the pancreatic β-cell function and the high levels of pro-inflammatory cytokines were also normalized with FMT. FMT also resulted in decreased expression of cleaved Capsase- 3 and Bax and reduced apoptosis of pancreatic cells.[20] Another strategy that is being elucidated for T2DM treatment is the administration of SCFAs. Administration of SCFAs such as acetate in rats elicited an increase in the levels of plasma GLP-1 and PYY and reduction in inflammatory markers such as tumour necrosis factor-α (TNF-α).[21] A randomized trial in 60 patients showed that the SCFA, propionate, significantly increased the PYY and GLP-1 levels by 1.8 and 2.4 folds compared to basal secretion. Propionate supplementation also improved insulin sensitivity and resulted in a beneficial change in body weight and composition.[22] Probiotics and prebiotics have also been found to be promising for ameliorating T2DM. Treating diabetic rats with *Lactobacillus paracasei* NL 41 has been shown to remarkably improve blood glucose levels and insulin sensitivity. The probiotic treatment also reduced oxidative stress and conferred β-cell protection.[23] In a separate study, eight weeks of *Lactobacillus casei* 01 supplementation in T2DM patients showed decreased carbohydrate and fat intake, and improved glycaemic control.[24]

While the aforementioned treatment strategies targeting the microbiota are in the early stages of development, several current established T2DM treatments have also been reported to impact the gut microbiota, independent of their effects on glycemic control. For example, the anti-diabetic drug, metformin has been found to be a potent AMPK activator.[25] Treatment with acarbose, an α-glucosidase inhibitor has been evidenced to alter the composition of gut microbiota, with an increase in the gut content of *Bifidobacterium* and decrease in the concentrations of inflammatory cytokines, regardless of its glucose-lowering effects.[26] Further, the dipeptidyl peptidase-4 inhibitors, sitagliptin and vildagliptin have been found to increase the abundance of SCFA-producing bacteria in the gut microbiota and reduce the ratio of the phyla *Firmicutes/Bacteroides* in experimental models.[27,28]

2.2. Gut microbiota and hypertension

2.2.1. Pathogenetic mechanisms
Hypertension is another major and well-established risk factor for CVD. Studies have shown that hypertension is associated with an alteration in the composition of gut microbiota. In a research study elucidating the link between gut microbiota dysbiosis and hypertension, spontaneously hypertensive rats (SHR) were found to have a significantly different microbiome when compared to Wistar Kyoto rats (WKY). SHR had a 5-fold increase in *Firmicutes* to *Bacteroides* ratio compared with WKY. While WKY had an abundance of butyrate-producing bacteria including *Coprococcus* and *Pseudobutyrivibrio*; SHR had higher levels of lactate-producing bacteria, *Streptococcus* and *Turicibacter*. Furthermore, WKY had higher levels of two uncultured genera OTUs (109 and 177) (belonging to the *Bacteroidetes* phylum), which were absent in SHR. The gut microbiome of SHR was also characterized by higher levels

of other uncultured and *incertae sedis* bacteria genera OTUs (2761 and 3955) belonging to the *Firmicutes* phylum. In the same study, a 4-week course of the broad-spectrum antibiotic, minocycline was found to lower the mean arterial pressure significantly in an angiotensin II infusion model of hypertension. The reduction in blood pressure was accompanied by a decrease in the gut bacterial load. Treatment with minocycline decreased the *Firmicutes* to *Bacteroidetes* ratio. It also resulted in enrichment of acetate-producing bacteria such as *Akkermansia, Bacteroides, Enterorhabdus* and *Marvinbryantia*, thus highlighting the role of alteration of gut microbiota composition in the pathophysiology of hypertension.[29] Similarly, another experimental study by Adnan et al also proved an association between gut microbiota dysbiosis and systolic blood pressure (SBP). In this study, a significant increase in the *Firmicutes* to *Bacteroidetes* ratio was observed in hypertensive versus normotensive rats, and a negative correlation was noted between the abundance of the butyrate-producing family *Clostridiaceae* and acetate-producing genera *Holdemania* and *Coprobacillus* and SBP. The authors proposed that alteration of the gut microbiota composition may present a new strategy for the treatment of hypertension.[30] Other experimental and clinical studies have also confirmed similar associations between microbial content and blood pressure (BP) regulation.[31,32] A very recent study conducted in Brazil involving 48 hypertensive and 32 normotensive subjects showed a significantly increased *Firmicutes* to *Bacteroidetes* ratio in hypertensive individuals. More than half of the hypertensive individuals had a high inflammatory score. Further, it was observed that the hypertensive individuals had a higher TNF-α/IFN-γ ratio compared to the normotensive group.[33]

Several mechanisms have been elucidated to explain the association between alteration in gut microbiota composition and BP regulation, including the role of SCFAs. SCFAs exert a plethora of actions via G protein-coupled receptors such as vascular olfactory receptor 78 (Olfr78) and G protein-coupled receptor 41 (GPR41). While GPR41 activation by SCFAs such as propionate causes vasodilation and reduction in BP; at higher concentrations of SCFAs, Olfr78 activation results in elevation of renin levels and a counter increase in BP to avoid hypotensive effects, thus facilitating BP regulation.[34] In addition to direct effects on vasodilation, SCFAs have also been linked to BP regulation indirectly through plasminogen activator inhibitor-1 (PAI-1). PAI-1 levels have been positively correlated with BP and inflammation and a negative correlation has been noted between PAI-1 levels and abundance of butyrate-producing microbiota, which explains an indirect effect of gut microbiota alteration in BP regulation.[32]

2.2.2. Therapeutic implications

Several studies have explored the usefulness of drug interventions altering the gut microbiota composition and/or their metabolites on BP modulation. Gomez-Arango et al evaluated the effect of probiotic administration in SHR. Treatment with *Lactobacillus fermentum* CECT5716 (LC40) or a 1:1 mixture of *L. coryniformis* CECT5711 and *L. gasseri* CECT5714 (K8/LC9) for 5 weeks resulted in a significant increase in the counts of *Lactobacillus* spp. These effects were more intense in those animals treated with K8/LC9 compared to LC 40. Probiotic treatment also reduced the vascular levels of reactive oxygen species, vascular inflammation and improved endothelial function in the SHR group.[35] In another experimental study, the intake of milk fermented using probiotic bacterial strains such as *Lactobacillus casei* TMC0409 and *Streptococcus thermophilus* TMC1543 for 8 weeks was associated with a significant lowering of BP compared to treatment with placebo.[36] TMC1543 antibiotic administration has also been shown to lower arterial BP in a case report of a 69-year old lady with resistant hypertension. The patient's BP was controlled for two weeks while she was taking antibiotics and was off antihypertensives. An additional six months of satisfactory BP control was obtained with the use of just one antihypertensive medication.[37]

2.3. Gut microbiota and dyslipidaemia/obesity

2.3.1. Pathogenetic mechanisms

The association between dyslipidaemia, obesity and CVD is well-established in the literature. Several studies have elucidated the association between gut microbiota and alterations in lipid metabolism/obesity.

Gut microbiota has been found to have a strong influence on the levels of plasma cholesterol. Bacteria belonging to the class *Betaproteobacteria*, and *Bacteriodales* and phylum, *Firmicutes* have been found to be significantly high in experimental high-cholesterol models.[38] Further, a study by Ley et al in obese subjects showed that *Firmicutes* dominate the gut microbiota in obese people, while *Bacteroidetes* remain the abundant bacterial group in lean subjects. Also, diets restricted in carbohydrates and fats were shown to increase the proportion of the genus, *Bacteroidetes* in this study.[39]

Several mechanisms have been postulated to explain the effects of gut microbiota on lipid metabolism and obesity, that involve production of SCFAs, and regulation of secondary bile acids, trimethylamine (TMA)/trimethylamine N-oxide (TMAO) and pro-inflammatory mediators such as lipopolysaccharides:

- Activation of GPR43 by SCFAs has been proposed to prevent fat accumulation.[17] Further, SCFAs have also been shown to activate peroxisome proliferator (PPAR)-γ,[18,40] and increase plasma PYY and GLP-1 levels,[22] resulting in increased energy expenditure, and reduced body weight and accumulation of triglycerides.
- Gut microbiota has also been found to influence the deconjugation and excretion of bile acids that regulate lipid metabolism through farnesoid X receptor (FXR) and Takeda G-protein coupled bile acid receptor (TGR5) signalling.[41,42]
- Paradoxically, TMA and TMAO generated by specific microbiota may promote an increased risk of atherosclerosis and CVD through mechanisms involving lipid metabolism and inflammation.[41]
- Reduced gut permeability by specific gut microbiota may prevent the translocation of endotoxins such as lipopolysaccharides into the blood and prevent associated inflammation. It may be pertinent to mention here that lipopolysaccharides have been proven to be associated with the development of atherosclerosis and CVD.[41]

2.3.2. Therapeutic implications

Several studies have translated the pathophysiological association between gut microbiota and lipid metabolism/obesity for the development of therapeutic strategies addressing these disease states. Co-supplementation with *Lactobacillus fermentum* MTCC: 5898-fermented milk in a rodent model was found to improve the lipid profile, atherogenic index, coronary artery disease (CAD) risk index and the serum levels of various pro-inflammatory cytokines.[43] Further, a meta-analysis by Wu et al also highlighted a beneficial role of the probiotic *Lactobacillus* in significantly reducing total cholesterol and low-density lipoprotein cholesterol.[44] In addition to probiotics, existing therapeutic strategies for dyslipidaemia and obesity have also been explored for association of their efficacy with mechanisms involving the gut microbiota. Lai et al proved that the beneficial effects of diet and exercise in controlling body weight are transmissible through FMT, thus highlighting a plausible role of gut microbiota in the effects of these interventions on obesity.[45] In an experimental study, statins

significantly increased the abundance of genera *Bacteroides, Butyricimonas* and *Mucispirillum,* and this gut microbiota alteration correlated with metabolic improvements.[46] Further, in a systematic review, a considerable alteration in the gut microbiota after bariatric surgery was noted with an increase in bacteria belonging to four phyla, including *Bacteroidetes, Fusobacteria, Verrucomicrobia* and *Proteobacteria,* thus suggesting a possible link between gut microbiota and metabolic alterations in humans.[47]

3. Gut microbiota and cardiovascular diseases

In addition to indirect effects on various CVD risk factors such as T2DM, hypertension, dyslipidaemia and obesity, as elaborated above, gut microbiota dysbiosis has been found to have direct implications on cardiovascular health. Factors such as oxidative stress, systemic and vascular inflammation contribute to the genesis and progression of CVD. These factors have been found to have a strong link with gut microbiota dysbiosis. The role of gut microbiota dysbiosis in atherosclerosis and CAD, chronic heart failure (CHF) and atrial fibrillation (AF) and associated therapeutic implications have been discussed in detail below.

3.1. Role of gut microbiota in atherosclerosis and CAD

3.1.1. Pathogenetic mechanisms
Several studies have highlighted the presence of an altered gut microbiota in patients with atherosclerosis and CAD. A study by Cui et al that involved high-throughput screening of stool samples of patients with coronary heart disease (CHD) and healthy controls revealed that CHD patients had a significantly greater α-diversity than that of controls. Patients with CHD had an abundance of the phyla, *Firmicutes* compared to the controls, while *Bacteroidetes* was the most prominent group in controls. *Clostridia* was the most prominent in the phylum *Firmicutes* and was higher in CHD patients when compared to controls. Further, CHD patients also showed a decrease in *Proteobacteria* and an increase in *Fusobacteria* compared with the control group.[48] In a separate experimental study by Chan et al elucidating the effect of probiotics and telmisartan in improving high-fat induced atherosclerosis, it was noted that high-fat diet resulted in an increase the *Firmicutes* to *Bacteroidetes* ratio. High-fat diet also lowered the abundance of *Eubacterium, Anaeroplasma, Oscillospira, Roseburia* and *Dehalobacterium,* and increased the levels of *Allobaculum, Clostridum, Lactobacillus* and *Bifidobacteria.* Further, a negative correlation was observed between the reduction in: (1) *Eubacterium* and increase in inflammatory cytokines such as matrix metalloproteinase −9 (MMP-9) and E-selectin; (2) *Dehaobacterium* and adipocyte fatty acid binding protein (A-FABP); and (3) *Roseburia* and MMP-9, thus confirming an association between gut microbiota dysbiosis and atherosclerosis.[49]

Multiple mechanisms have been proposed to explain the link between gut microbiota dysbiosis and the pathogenesis of atherosclerosis and CAD, including induction of systemic inflammation, generation of harmful metabolites that may exert proatherogenic effects, alteration of lipid metabolism and infection. The key molecules that mediate these mechanisms include cytokines, toll-like receptors (TLR), SCFAs, bile acids, lipopolysaccharides and TMAO.[50] In homeostatic conditions, TLRs present on the gut epithelial and dendritic cells recognize microbe-associated molecular patterns (MAMPs) and stimulate cytokine production. This, in addition to maintenance of tight barrier function of the epithelium by selected microbiota and prevention of leakage of lipopolysaccharides into the blood help regulate innate immune processes.[50] Further, SCFAs produced by specific microbiota, through inhibition of NK-κB exhibit strong anti-inflammatory properties.[51]

Dysbiosis in the gut microbiota may interfere with these pathways and influence the risk of CVD. An increase in lipopolysaccharides due to dysbiosis may induce TLR4 signalling and result in myocarditis.[50,52] In experimental studies, certain strains of *Lactobacillus* have been found to inhibit the TLR4 pathway.[53] Further, a negative correlation has been identified between C−C chemokine receptor type 2 (CCR2) expressed on monocytes and increase in *Bifidobacterium*[54]; and CCR2 has a positive association with inflammation in the arterial wall.[55]

Paradoxically, gut microbial metabolites such as TMAO might play an important role in the formation of atherosclerotic plaques. In a study involving 1876 stable subjects, it was observed that increased levels of choline TMAO and betaine showed dose-dependent associations with the presence of CAD and myocardial infarction. The study also demonstrated a positive correlation between plasma levels of TMAO and atherosclerotic plaque size. The levels of FMO3, an enzyme involved in TMAO production were inversely correlated with the plasma levels of the protective high-density lipoprotein (HDL) cholesterol levels. Inhibition of gut microbiota was shown to inhibit macrophage foam cell formation induced by choline.[56] However, the prevalence of TMA-producing gut microbiota has been found to be low and may be confined to specific strains of *Clostridia, Eubacteria* and *Escherichia coli*.[57]

3.1.2. Therapeutic implications
Intake of probiotics has shown to be effective in the management of atherosclerosis and CAD. Kawase et al demonstrated that administration of fermented milk with both *Lactobacillus casei* TMC0409 and *Streptococcus thermophilus* TMC1543 in rodents resulted in a significant decrease in the atherogenic index compared with the control group. It was also observed that the intake of fermented milk was associated with a significantly lower levels of serum total cholesterol than the control group.[36] A recent study involving administration of *Lactobacillus rhamnosus* GG supplements in patients with CAD for 12 weeks resulted in a significant reduction in the TMAO and pro-inflammatory cytokine levels.[58] In the study by Chan et al in which apolipoprotein E knockout mice were fed with high fat diet to induce atherosclerosis, while treatment with both *Lactobacillus rhamnosus* GG and telmisartan was effective in reducing the size of atherosclerotic plaques, telmisartan was more effective than *Lactobacillus* in lowering the *Firmicutes* to *Bacteroidetes* ratio.[49]

3.2. Role of gut microbiota in chronic heart failure

3.2.1. Pathogenetic mechanisms
Chronic heart failure is another important CVD that has been investigated for association with gut microbiota. In a comparative study involving 60 patients with both mild (New York Heart Association [NYHA] functional class I to II) and moderate to severe (NYHA functional class III to IV) CHF, the gut microbiota of CHF patients was found to be significantly different from that of the healthy controls. Patients with severe CHF exhibited increased levels of *Candida, Campylobacter,* and *Shigella* species in faecal samples. However, there were no major differences for saprophytic microorganisms and commensal strains between the control group and CHF patients, and between patients with mild and moderate to severe CHF. The intestine permeability was found to be higher in patients with moderate to severe CHF compared with those with mild CHF.[59] Another study involving 53 CHF patients and 41 healthy controls reported that CHF patients were characterized by increased levels of *Ruminococcus gnavus, Streptococcus* sp. and *Veillonella* sp, while controls had an abundance of *Faecalibacterium prausnitzii, Oscillibacter* sp. and *Sutterella wadsworthensis*. The gut microbiota in CHF patients also expressed higher levels of microbial

genes for lipopolysaccharide biosynthesis, tryptophan and lipid metabolism, especially TMAO production. Further, the proportion of bacteria involved in SCFA metabolism was lesser in CHF patients.[60]

Multiple mechanisms and mediators have been proposed to explain the link between gut microbiota and CHF. Heart failure patients with pedal oedema have been found to have higher concentrations of endotoxins and lipopolysaccharide/log lipopolysaccharide-binding proteins (LBP) ratio compared with those without oedema. The plasma concentrations of C-reactive protein, TNFα, soluble TNF receptor-1 and receptor-2, interleukin-6, and soluble CD14 have also been noted to be higher in oedematous heart failure patients compared with non-oedematous patients.[61] Tang et al demonstrated that patients with CHF had a higher median level of TMAO and BNP compared to controls; increased TMAO levels were found to be associated with increased 5-year mortality rates. A modest significant correlation was observed between TMA and BNP. High fasting TMAO levels were associated with a 2.2-fold increase in mortality risk even after adjusting for traditional risk factors and BNP and a 1.80-fold increase in mortality risk even after adjusting for traditional risk factors and BNP plus estimated glomerular filtration rate (eGFR).[62] Another mechanism is related to increased systemic inflammation in CHF patients. Heart failure is characterized by reduced cardiac output which compromises the blood flow to the intestinal wall,[63] thus disrupting the integrity of the gut wall allowing the gut contents to leak into the blood stream, which in turn triggers low-grade systemic inflammation.[28,64]

3.2.2. Therapeutic implications

Diuretics and probiotics have been studied for microbiota-related effects in CHF patients. Short-term diuretic therapy has been found to be associated with a decrease in endotoxin levels while the cytokine levels remained unaltered.[61] The ability of probiotic strains to boost the gut wall integrity and inhibit inflammation might be helpful in preventing these events. Further, probiotic therapy with *Lactobacillus rhamnosus* has been shown to decrease systemic inflammation and the levels of TMAO,[58] which might be beneficial in CHF patients.

3.3. Role of gut microbiota in atrial fibrillation

3.3.1. Pathogenetic mechanisms

Another important CVD with evolving recent research related to gut microbiota is AF. Zuo et al compared the gut microbiome of patients with AF with that of healthy controls. They found that the gut microbiota of patients with AF was characterized by overgrowth of harmful bacteria. There was dramatic difference in 574 genera between the AF patients and healthy controls. Patients with AF had higher proportions of *Streptococcus*, *Enterococcus*, *Blautia*, *Dorea*, *Veillonella* and *Eubacterium*. Bacterial groups such as *Bifidobacterium*, *Roseburia* and *Ruminococcus* were also high AF patients compared with healthy controls. *Escherichia coli* was the most abundant pathogenic bacterial species found in AF patients. The levels of butyrate-producing species such as *Faecalibacterium prausnitzii* was low in patients with AF. There was a dramatic decrease in the abundance of *Fecalibacterium, Prevotella, Alistipes, Oscillibacter* (genus level), and *Sutterella* in AF patients compared with controls. A similar shift was observed for *Butyricicoccus, Flavonifractor,* and *Bilophila* as well. Alterations were also observed in 27 metabolites in the serum and stool samples of patients with AF; 14 metabolites including cholic acid, oleic acid, linoleic acid, and α-linolenic acid were found to be reduced in AF patients.[65]

Another study conducted on 12 patients with persistent AF >12 months (Pers >12 months) and 8 patients with persistent AF < 12 months (Pers <12 months) showed a remarkable difference in the gut microbiota of the two groups. While the levels of *Butyricicoccus* and *Paraprevotella* were lower in patients with longer persistent AF duration, the levels of *Blautia, Dorea,* and *Coprococcus* were found to be higher in these patients. Pers >12 months group also showed increased levels of *Thermosinus, Anaeroarcus, Clostridium bolteae,* and *Enterococcus faecium.* The abundance of genera such as *Faecalibacterium* and *Corynebacterium*, and species like *Faecalibacterium prausnitzii,* and *Eubacterium* sp. CAG 581 were increased in the Pers <12 months group. Further, it was found that prolonged AF duration significantly reduced the levels of choline. Choline also displayed a negative association with *Enterococcus faecium.* Metabolites such as phosphohydroxy pyruvic acid and 3-indoleacetic acid were decreased in Pers>12months and negatively correlated with persistent AF duration. The Pers <12months-enriched genus *Anaeroarcus* showed a positive correlation with the genus *Mycobacterium* decreased in the Pers<12months group.[66]

Recently another comparative study was carried to elucidate the difference in gut microbiota in patients with paroxysmal atrial fibrillation (PAF), persistent atrial fibrillation (psAF) and healthy controls. It was observed that the PAF and psAF groups had a striking similarity in the gut microbial profile. Both PAF and psAF patients were also associated with a higher *Firmicutes/Bacteroidetes* (F/B) ratio independent of factors such as age, BMI, hypertension, or T2DM. It was also observed that the relative abundance of *Firmicutes* and *Bacteroidetes* were similar in PAF and psAF groups but were significantly different from the control group. The study also revealed that PAF- and psAF-enriched metabolites, such as chenodeoxycholic acid (CDCA), were positively correlated with AF-enriched bacterial genera such as *Ruminococcus* and *Streptococcus*. A positive correlation was seen between the psAF-enriched serum choline and psAF-enriched family *Holosporaceae* and genus *Holospora*, genus *Methylovulum* and species *Methylovulum miyakonense*. Additionally, it was observed that the atrial diameter parameters in the PAF and psAF groups showed a significant correlation with one family (Holosporaceae), two genera (*Methylovulum* and *Holospora*), and five other bacterial species.[67] All these studies clearly indicate a role of gut microbiota in the pathogenesis and persistence of AF.

3.3.2. Therapeutic implications

TMAO plays an important role in the pathogenesis of CVD including AF. TMAO has shown to exacerbate autonomic activity and release of inflammatory cytokine in animal models of AF.[68] These effects may be inhibited by probiotics. However, there is lack of studies which have evaluated the effect of modulation of gut microbiota by treatments used for AF.

3.4. Gut microbiota and chronic kidney disease

3.4.1. Pathogenetic mechanisms

Gut microbiota is also altered in patients with CKD. Evidence suggests decreased intake of dietary fibre, constipation, impaired protein metabolism and medication as the major contributing factors of dysbiosis in CKD.[69] In CKD, structural and functional modifications of the gut-microbiota and impaired gut barrier function result in gut microbiome dysbiosis. Subsequently, this leads to the production of excessive quantities of uremic toxins which may get retained due to decreased urinary excretion in CKD. These toxins are derived from the unbalanced metabolism of nitrogen compounds mostly in association with the nondigestible carbohydrates, such as p-cresyl sulphate and indoxyl sulphate. They get translocated into systemic circulation via impaired gut barrier and may worsen CKD. They are also implicated in the development of CVD and risk of death in CKD patients.[70,71]

Effects in Diabetes Mellitus

- ↑ production of anti-inflammatory cytokinesis and chemokines and ↓ oxidative stress in pancreatic β-cells.
- ↓ expression of pro-inflammatory markers.
- ↑ AMPK activation and ↓ get permeability.
- ↑ production of SCFAs.
- ↑ PYY production.
- ↑ GLP-1 production.
- ↑ insulin sensitivity and glycemic control.

Effects in Atherosclerosis and Coronary Artery Disease

- ↓ vascular inflammation by NF-kB and TLR4 pathway inhibition.
- ↓ CCR2 expression in monocytes
- ↓ MMP-9 production.

Effects of Hypertension

- BP regulation: ↓ BP through GPR41 activation and ↑ vasodilation; counter ↑ BP through Olf 78 activation to prevent hypotension.
- Improved endothelial function.
- ↓ vascular inflammation.

GUT MICROBIOTA

SCFA and other microbiota derived metabolites

Effects in Chronic Heart Failure

- ↑ gut wall integrity → ↓ leaky gut-induced systemic inflammation.
- ↓ TMAO production
- ↓ CRP, TNF-α, IL-6 and soluble CD14 expression.

Effects in Dyslipidaemia and Obesity

- Formation of hypotension bile acid pool and ↑ excretion of bile acids that regulate lipid metabolism by FXR and TGR5 signalling.
- GPR43 activation → inhibition of fat accumulation.
- Activation of PPAR-γ; ↑ PYY and GLP-1 levels → ↑ energy expenditure; ↓ body weight.
- ↓ get permeability and ↓ LPS in blood.

Effects in Atrial Fibrillation

- ↓ TMA O production
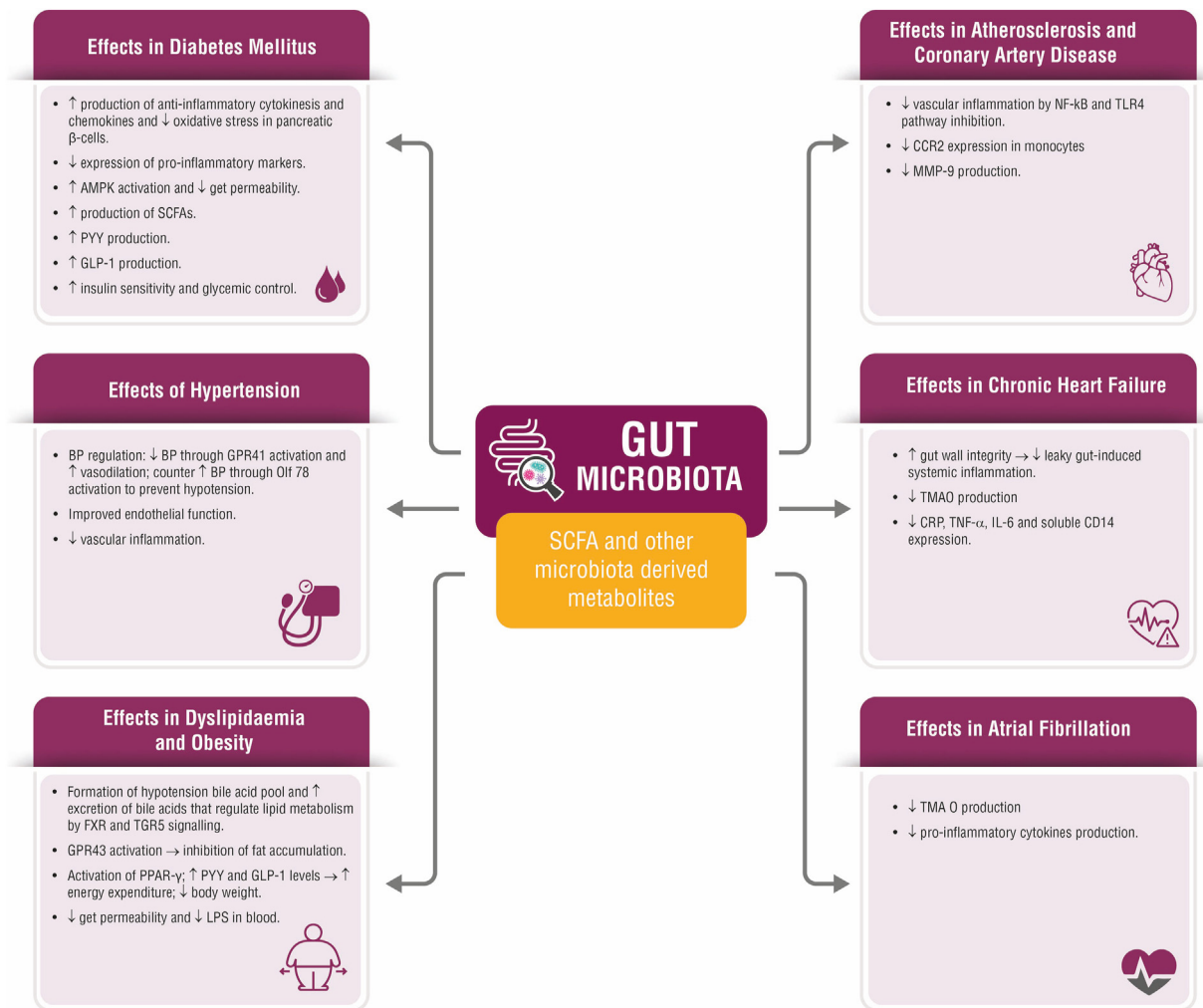- ↓ pro-inflammatory cytokines production.

Fig. 1. Summary of the effects of gut microbiota in ameliorating various CVDs and CVD risk factors.

Indoles are intestinal bacterial metabolites of tryptophan, which are metabolized into indole indoxyl sulphate (IS) and indole-3-acetic acid (IAA). They activate nuclear factor (NF)-Kb and plasminogen activator inhibitor type1 and are culprits in tubulointerstitial fibrosis, aortic and vascular calcification, endothelial lining damage and decreased production of erythropoietin. P-Cresyl sulphate (PCS), another uremic toxin, is derived from the bacterial breakdown of tyrosine and phenylalanine that are subsequently sulphonated into PCS in the liver. They tend to cause renal fibrosis, oxidative stress and generation of inflammatory mediators.

Overall evidence indicates that increased levels of IS, IAA and PCS are associated with all-cause mortality and increased risk of cardiovascular events.[71] Trimethylamine N.

Oxide (TMAO) is generated via choline metabolism to trimethylamine gas that subsequently oxidates into TMAO in the liver. They are dependent on renal elimination, and hence, the serum levels of TMAO are elevated in CKD. Similar to aforementioned uremic toxins, TMAO has been implicated in the progression of renal insufficiency and increased mortality in patients with CKD.[71,72] Other uremic toxins, such as amines polyamines, D-amino acids, endotoxins, blood urea nitrogen (BUN) urea and their products, are also reported to be nephrotoxic and are implicated in the progression of CKD or CVD.[71]

3.4.2. Therapeutic implications

Intake of prebiotics and probiotics has been shown to be effective in reducing uremic toxin levels and slow the progression of CKD and prolong life. Meijers et al observed that serum concentrations of PCS and IS were reduced post oral intake of p-inulin, a prebiotic in haemodialysis patients.[73] Similarly, Evenepoel et al reported reduction in PCS levels post treatment with acarbose in healthy persons.[74] In haemodialysis patients, treatment with oral *Lactobacillus acidophilus* decreased levels of uremic toxins such as serum dimethylamine.[75] Several novel therapies such as lubiprostone, a prostaglandin derivative and 3, 3-dimethyl-1-butanol (DMB), a trimethylamine (TMA) inhibitor, have shown beneficial

Table 1
Therapeutic Interventions related to Gut microbiota for Cardiometabolic diseases.

Diabetes Mellitus			
Study	Intervention	Patients	Comments
Vrieze et al.[80] deGroot et al.[81] RCT	FMT	Individuals with MS	Improves insulin sensitivity
Chambers et al.[22]	SCFA (Propionate)	Overweight individuals	Stimulates glucose metabolism Improves insulin sensitivity
Bock et al.[82] Meta-analysis	*Lactobacillus, Bifidobacterium* and *Streptococcus* strains	Individuals with diabetes	Decreased FPG and insulinaemia
Hypertension			
Bartolomaeus et al.[83]	SCFA (Propionate)	Angiotensin II infused wild-type NMRI mice,	Reduction in BP
Khalesi et al.[84] Meta-analysis	Probiotics of *Lactobacillus, Bifidobacterium, Saccharomyces, Enterococcus* and *Streptococcus* strains	Individuals with or without hypertension	Significant reduction in BP, especially improvement in lower baseline BP. Significant decrease with long-term intervention
Dyslipidaemia/obesity			
Jung et al.[85] RCT	Probiotics of L. *gasser*	Overweight and obese adults	Significant reduction in BMI, waist and hip circumference
Pedret et al.[86] RCT	Probiotics of *B. animalis*	Abnormal overweigh adults	Significant reduction in BMI, abdominal visceral fat and hip circumference
Reimer et al.[87] RCT	Prebiotics of Inulin-type fructans	Overweight and obese adults	Patients reported outcomes of subjective hunger rating and subjective satiety rating is increased. Energy and carbohydrate consumption are also reduced
Ruscica et al.[88] Meta-analysis	Co-administration of *Bifidobacterium/yeast* extract	Individuals with moderate hypercholesterolemia	Decrease in total cholesterol, LDL and triglycerides as well as an increase in HDL
Atherosclerosis and CAD			
Moludi et al.[58]	Weight loss diet along with probiotics supplementation LGG	Individuals with CVD	Improved endotoxemia, by reducing the LPS and TMAO levels. Also improved microbiota profile
Kawase et al.[36]	*L. casei* TMC0409 and *S. thermophilus* TMC1543	Rodents	Significant decrease in the atherogenic index
Chen et al.[89]	*L.acidophilus*	ApoE$^{-/-}$ mice	Decrease in Atherosclerotic burden
Chronic Heart failure			
Contstanza et al.[90] RCT	Probiotics of *S. boulardii*	Patients with NYHA II and III, CHF and EF <50%	Improvement in ventricular function Decrease in inflammatory biomarkers
Uremic toxins			
Ranganathan et al.[91]	*S. thermophilus, L. acidophilus,* and *B. longum*	Patients with CKD	Reduction in BUN
de Preter et al.[92]	Oligofructose-enriched inulin	Healthy individuals	Decrease in p-cresol

BP: Blood pressure; BMI: Body mass index; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CHF: Congestive heart failure; CKD: Chronic kidney disease CVD: Cardiovascular disease; EF: Ejection fraction; FMT: Fecal Microbiota Transplantation; FPG: Fasting plasma glucose; HDL: High-density lipoproteins; LDL: Low-density lipoproteins; LGG: Lactobacillus rhamnosus GG; LPS: Lipopolysaccharide; MS: Metabolic syndrome; NHYA: New York Heart Association; RCT: Randomized clinical trial.; SCFA: Short chain fatty acids; TAMO: Trimethylamine N-oxide.

effects in pre-clinical studies. Lubiprostone has been shown to improve the microbiota profile with a rapid increase in the *Saccharolytic* species and reduce the BUN levels.[76] Further, 3, 3-dimethyl-1-butanol that is found in some essential oils has been shown to reduce the levels of TMAO in addition to the inhibition of macrophage foam cell and atherosclerotic lesion development.[77]

An overview of the various mechanisms of gut microbiota in ameliorating CVD risk factors such as T2DM, hypertension, dyslipidaemia and obesity; and CVDs such as atherosclerosis, CAD, CHF and AF is shown in Fig. 1. With respect to treatment, the European and American guidelines recommend metformin (unless contraindicated or not tolerated) or sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP) receptor agonists for glycaemic management in established atherosclerotic CVD or CKD. These medications are also recommended for weight loss along with lifestyle interventions.[78] Other drugs for weight loss are endocannabinoids, phentermine in combination with topiramate, liraglutide, and naltrexone in combination with bupropion.[79] The latest European Society of Cardiology. ESH: European Society of Hypertension (ESH-ESC) guidelines for hypertension recommended renin–angiotensin system (RAS) blockers and calcium

antagonists as the first-line treatment for metabolic syndrome in patients not attaining target BP of less than 140/90 mmHG with lifestyle changes.[80] Agents such as telmisartan that act at peroxisome proliferator-activated receptor gamma (PPAR-γ) may have beneficial role in controlling BP and managing metabolic syndrome. Pharmacotherapy, particularly statins, have been effective in the management of dyslipidaemia in metabolic syndrome setting. Both high-dose statins or moderate-intensity statins have been found beneficial in managing dyslipidaemia. Newer drugs including apolipoprotein B may be used as secondary treatment in patients with high triglyceride levels and low HDL-C levels. Alirocumab, a monoclonal antibody, has also been shown to reduce LDL-C levels in patients receiving statins.[79] Table 1 summaries the therapeutic intervention related to gut microbiota such as prebiotics, probiotics, diet modification and FMT in each cardiometabolic disease.

4. Conclusion

There is a growing body of evidence, which suggests that there is a clear association between gut-microbiota dysbiosis and CVDs, CVD risk factors and CKD-related complications discussed in this

review. Modern molecular techniques have enabled the characterization of gut-microbiota and elucidation of their protective mechanisms in these disease states. Translation of this knowledge into useful therapeutics such as FMT, probiotics, and diet therapies has been proven to be safe and effective for the management of CVDs and associated risk factors and CKD and associated complications. Both animal and human studies evaluating the efficacy of gut-microbiota-modulating therapies have shown promising results. However, implementation of such therapeutic strategies entails a more lucid understanding of the role of the gut-microbiota in the pathogenesis of CVDs and associated risk factors through large-scale, controlled trials in humans.

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