Current Hypertension Reports (2020) 22: 38
https://doi.org/10.1007/s11906-020-01046-0

HYPERTENSION AND THE KIDNEY (RM CAREY, SECTION EDITOR)

The Emerging Role of Gut Dysbiosis in Cardio-metabolic Risk Factors for Heart Failure

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Published online: 8 May 2020

Abstract

Purpose of Review To summarize the recent evidence that supports a role for the gut microbiota, microbiota-derived metabolites, and dysbiosis on cardiovascular risk factors, and to discuss the neuro-cardio-metabolic mechanisms that link gut microbiota and heart failure.

Recent Findings There is growing evidence that the gut microbiota communicates with and impacts the cardiovascular system, contributing to the development of heart failure once it becomes out of balance (i.e. gut dysbiosis). The exact mechanisms of how the gut microbiota influences cardiovascular outcomes are not fully understood, but immune dysregulation and disturbance of neuro-enteroendocrine hormones seem to be involved. The disturbances in the gut microbiota influence the progression of several risk factors for heart failure, including atherosclerosis, obesity, diabetes, kidney disease and hypertension. In turn, these conditions also act to regulate the gut microbiota through the deterioration of the integrity of the intestinal barrier and the release of neurotransmitters and gastrointestinal hormones. In normal and healthy physiological conditions, these interactions are homeostatic and tightly controlled. However, a combination of environmental exposures (e.g. antibiotics use and Western diet) and the host's intrinsic conditions (e.g. genetics and fluid status) can result in the breakdown of intestinal homeostasis and further progression of cardiovascular risk factors, which lead to the development of heart failure.

Summary Manipulation of the gut microbiota may have the potential to improve cardiovascular outcomes by ameliorating immune system dysregulation, enteroendocrine disruptions, and neurohormonal activation in patients with cardiovascular risk factors for heart failure.

Keywords Gut microbiota · Gut microbiome · Metabolites · Dysbiosis · Hypertension · Heart failure · Cardio-metabolic

This article is part of the Topical Collection on *Hypertension and the Kidney*

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Introduction

The intestinal tract is the largest endocrine-neurohormonal network in the human body, and the gut microbiota plays a key role in maintaining its homeostasis. [1] One of the important roles of the gut microbiota is to digest food to harvest nutrition and energy for the host. Some types of fibre are prebiotic and, while resistant to digestion in the upper gastrointestinal tract, they are fermented by the commensal bacteria in the large intestine as their main energy source. In this context, the majority of the intestinal bacteria exist in a mutualistic fashion with the host to provide energy, metabolites, and vitamins. [2]

Another important role of the gut microbiota is to prime the immune system. [3] Fermentation of prebiotic fibre by the gut microbiota leads to the release of metabolites, especially the short-chain fatty acids (SCFAs) acetate, propionate, and butyrate. Amongst their many functions, they can bind to G

protein–coupled receptors (GPCRs, such as GPR41, GPR43, and GPR109A) and have a role regulating the immune system and inflammation. [4] Destruction of gut microbial balance can trigger allergic reaction and inflammation by breakdown of the intestinal epithelial barrier and shifting the macrophage polarization, for example. [5–7] This is supported by the evidence that both GPCR-deficient mice and germ-free mice (which have little or no SCFAs) had an exacerbated or a poorly resolving inflammation in various models such as colitis, arthritis, asthma, and diabetes. [4, 8]

A change in gut microbial composition was also observed in experimental hypertensive models, [9] which have smaller populations of bacteria that produce SCFAs [10•, 11]. Hypertensive models also have reduced number of mucus-producing Goblet cells and gut epithelial junctional proteins, which together with lower levels of SCFAs lead to increased intestinal permeability. [5] This is known as gut dysbiosis, defined as alterations to the gut microbiome and breakdown of the gut epithelial barrier, and is a growing concept in all aspects of cardiovascular disease (CVD). While advances in microbial sequencing, metabolomics and bioinformatics techniques have partially revealed the crosstalk of dysfunctional host-microbiome interactions in CVD, the exact mechanisms remain unknown. Heart failure is the most advanced stage of CVD with a 12-month re-hospitalization rate of 44%, and mortality rate at 1 year as high as 17%. [12, 13] Importantly, all traditional risk factors for CVD and, relevant to this review, heart failure, including atherosclerosis, obesity, diabetes, kidney disease, and hypertension, have been associated with changes in the gut microbiota. [14••, 15] In this review, we discuss the known and putative mechanisms that link the gut microbiota to cardio-metabolic risk factors for the development of CVD with a focus on heart failure.

Diversity of Gut Microbiota

There are several factors that can affect the gut microbiota including diet, antibiotics, age, host's genetics, and conditions such as inflammatory bowel disease which significantly affect abundance and diversity of microbiota. [6, 16, 17] The current line of evidence supports that the first major microbial colonization takes place at birth, with diet subsequently having the greatest impact in defining the shape, structure, and diversity. [18] The diversity of microbial bacteria is typically assessed in number (richness and abundance) and distribution (evenness). High intake of vegetables at both short and long term, for example, is associated with higher microbial diversity. [19, 20] This is relevant as human studies have suggested that greater alpha diversity (i.e. quantitative scores of the number and prevalence of microbes per sample) is usually associated with health status. [10•] Beta diversity (i.e. qualitative scores based on how similar or distant the microbial composition is in one environment compared with another) are also useful to determine whether certain microbial profiles are associated with phenotypes (e.g. diet intake) and disease states (e.g. hypertension). These scores can be estimated from both amplicon (i.e. 16S) or metagenomics sequencing. We refer the reader to a recent review and guidelines on these analyses, interpretation, and reporting. [21]

Overuse and overprescription of antibiotics in recent years have become more common and of great concern worldwide. Antibiotics affect the diversity of the gut microbiota, removing certain species and disturbing microbial communities. Clindamycin, for example, decreases the population of bacteria from the genus *Bacteroides*, while clarithromycin supresses *Acinetobacter*. [22] Vancomycin is the most commonly used antibiotics for *C. difficile* infection and results in the depletion of *Bacteroides*, *Ruminococcus*, and *Faecalibacterium*, and an increase in Proteobacteria species, and can lead to recurrent *C. difficile* infection. [23]

Gut Dysbiosis as an Enteroendocrine-Neurohormonal System Disorder

Besides the important role the gut microbiota has on food digestion, it also serves as a virtual endocrine organ. Increasing evidence supports the metabolic capacity of the gut microbiota to produce enteroendocrine and neurohormonal peptides that reach the circulation and regulate the function of multiple organs and systems (Fig. 1). [24] The putative pleiotropic endocrine effects of gut microbiota are characterized by a number of endogenous hormones and their receptors localized in multiple organs and cell types. [25, 26]

Microbial metabolites such as SCFAs work not only as an important source of energy but also as signalling molecules to regulate the host's metabolism, central nervous system, and cardiovascular system. [24, 27] The gut microbiota releases neurotransmitters (serotonin, dopamine, noradrenaline) and gastrointestinal hormones (ghrelin, leptin, glucagon-like peptide-1) to indirectly regulate multiple organ function. [26, 28, 29]

The microbiota also regulates the bioavailability of choline and its microbial-derived metabolites. Trimethylamine (TMA) is the gut microbial metabolic product of dietary phosphatidylcholine and carnitine. [16, 30] TMA is then absorbed from the intestine, and in the liver, TMA is oxidized by flavin monooxygenases, resulting in trimethylamine N-oxide (TMAO). TMAO promotes atherosclerosis, [16, 30] thrombosis, [31] adipogenesis, [32] and renal insufficiency. [33] For example, excessive intake of phosphatidylcholine was associated with increased TMAO production and development of atherosclerotic plaque in the aorta of an atherosclerosis-prone mouse model (C57BL/6J *Apoe*$^{-/-}$). [16] The suppression of

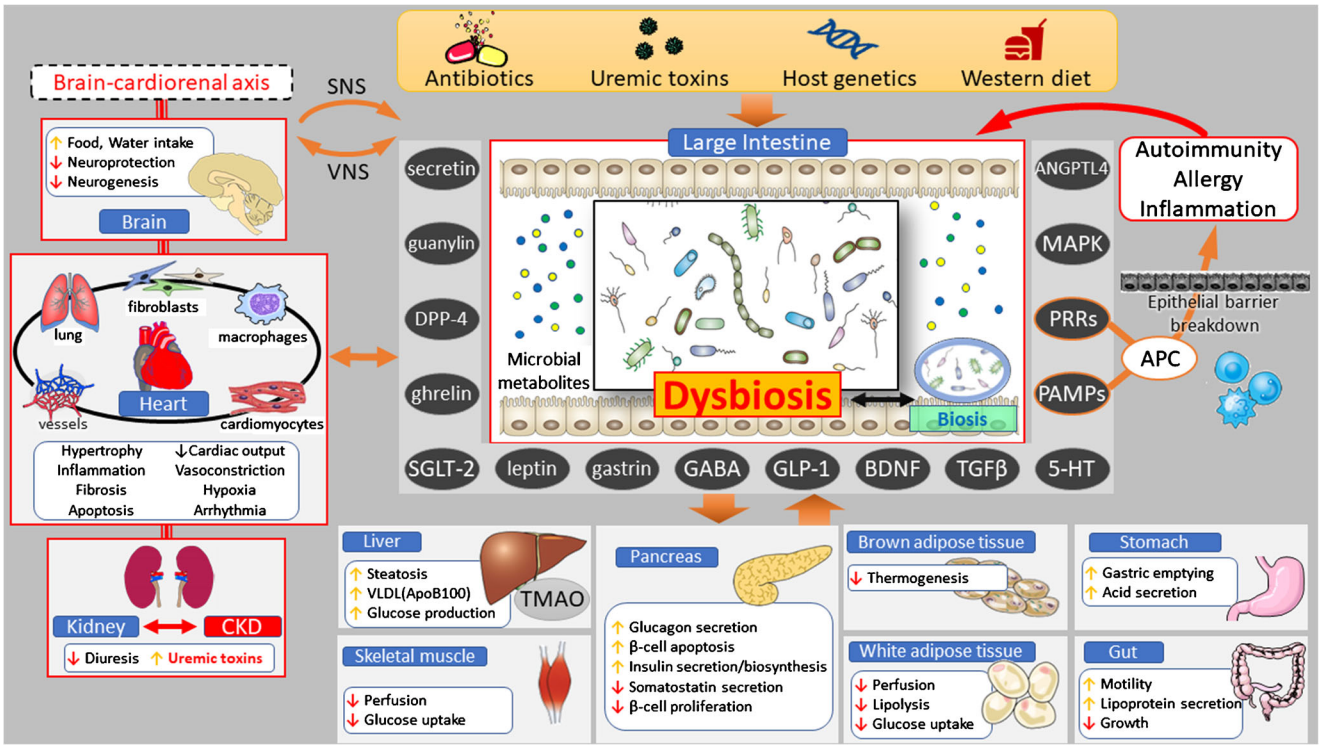

Fig. 1 Putative endocrinal and neurohormonal actions of gut microbiota and its metabolites in relation to cardio-metabolic risk factors for heart failure. The microbial metabolites such as short-chain fatty acids work not only as an important source of energy but also as a signalling molecule to regulate the host metabolism, central nervous system, and cardiovascular system. The gut microbiota also releases neurotransmitters (serotonin, dopamine, noradrenaline) and gastrointestinal hormones (ghrelin, leptin, glucagon-like peptide-1) to directly and indirectly regulate multiple organ function. The gut microbiota also regulates the bioavailability of choline, carnitine, and its metabolites, which have detrimental effects and lead to cardiovascular disease. SNS, sympathetic nervous system; VNS, vagus nerve system; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; GLP-1, glucagon-like peptide-1; BDNF, brain-derived neurotrophic factor; TGF β, transforming growth factor beta; ANGPTL4, angiopoietin-like protein 4; TMAO, trimethylamine N-oxide; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium glucose cotransporter 2; VLDL, very low-density lipoproteins; PRRs, pattern recognition receptors; PAMPs, pathogen-associated molecular patterns; APC, antigen presenting cell; CKD, chronic kidney disease

gut microbiota by broad-spectrum antibiotics inhibited macrophage foam cell formation induced by dietary phosphatidylcholine. [16] Moreover, plasma levels of TMAO and, more recently, trimethyllysine (a TMAO precursor) showed dose-dependent associations with CVD. [16, 34] Collectively, these results revealed the mechanistic association between nutrition, gut microbiota, platelet activation, and atherothrombotic risks.

Another interesting microbial-dependent molecule is angiopoietin-like protein 4 (ANGPTL4). ANGPTL4 is expressed in various organs such as fat tissue and heart, but is also produced in the intestine under the regulation of the gut microbiota. [35] ANGPTL4 has multiple functions, including as a potent inhibitor of lipoprotein lipase causing elevation of plasma triglyceride, and as a conventional, non-competitive inhibitor binding to lipoprotein lipase to prevent hydrolysis, thereby, reducing atherosclerosis development. [36]

In the bi-directional neurohormonal communication between the brain and the gastrointestinal tract, emerging evidence supports that the gut microbiota communicates with the brain via cytokine release from mucosal immune cells, [37, 38] via the secretion of gut hormones such as 5-hydroxytryptamine (5-HT; serotonin) from enteroendocrine cells, [39] or via afferent fibres of the vagus nerve. [40] On the other hand, increased sympathetic nervous system (SNS) outflow to the gut contributes to epithelial dysfunction leading to dysbiosis. [41, 42] The dysbiosis-induced change in microbial metabolites increases the production of 5-HT, which counteracts gut vagal afferent activity to the brain. 5-HT also plays a role in the cardioregulatory centre in the brain (nucleus tractus solitarius; NTS), which integrates visceral afferent signals essential for cardiovascular homeostasis. [43, 44]

Studies have demonstrated that there is also a bi-directional interaction between the gastrointestinal tract and the kidney (gut-renal axis). [10•, 45, 46] The gut microbiota contributes to the production of representative uremic toxins in the setting of chronic kidney disease. Potential regulatory links between the gut microbiota and the kidney might involve neurohormonal interactions. [47] Indeed, evidence supports that prebiotic (fibre) or postbiotic (acetate) treatment modulated the renal transcriptome in otherwise healthy animals. [10•]

The gut-derived incretin hormone glucagon-like peptide-1 (GLP-1) is produced from the intestinal L-cells upon meal

ingestion. GLP-1 can act through endocrine, paracrine, and neuronal pathways to maintain homeostasis in local and remote tissues and cell types. These effects are consistent with the widespread and abundant expression of the GLP-1 receptors. [1] The gut microbiota fermentation of specific prebiotics and other non-digestible carbohydrates is associated with the secretion of GLP-1 and involved in the regulation of energy balance and glucose homeostasis. [48] Manipulation of the GLP-1 pathway is of considerable interest in the management of type 2 diabetes and its complications. Interestingly, inhibition of DPP-4, which degrades GLP-1, has been shown to exert favourable effects on the gut microbiota and in clinical trials to reduce adverse micro- and macro-vascular outcomes by mediating putative gut-renal axis. [45, 49]

Sodium glucose cotransporter 2 (SGLT-2) inhibitors are the most recently approved class of anti-glycaemic agents and have demonstrated reduced cardiovascular and overall mortality. [50, 51] The inhibition of intestinal SGLT-2 can influence the gastrointestinal environment. Two-week treatment with the SGLT-2 inhibitor canagliflozin significantly reduced the plasma levels of p-cresol sulfate and indoxyl sulfate (uremic toxins), and also increased caecal SCFA production in diabetic mice, suggesting that canagliflozin inhibited production of p-cresol and promoted bacterial carbohydrate fermentation in the intestine. [45, 52] In a recently randomized control study, the SGLT-2 inhibitor dapagliflozin significantly reduced heart failure hospital admission and deaths even in non-diabetic heart failure patients with reduced ejection fraction. [50] Although how SGLT-2i improves cardiovascular outcomes, especially in non-diabetic subjects, is currently unclear, the pleiotropic effects of SGLT-2i suggest that the intestinal signalling from gut microbiota might regulate systemic metabolism and modulate neurohormonal activation beyond intestinal hormones.

Atherosclerosis

Atherosclerosis is characterized by chronic vascular inflammation often associated with metabolic diseases such as dyslipidemia, diabetes, and hypertension. As discussed above, metabolites of dietary lipid phosphatidylcholine (choline, carnitine, N-oxide, and betaine) contribute to the progression of atherosclerosis by promoting the upregulation of multiple macrophage scavenger receptors to initiate local inflammation. [16] This was the first discovery of the relationship between gut flora metabolites and atherosclerotic cardiovascular pathogenesis, indicating a potential therapeutic benefit of targeting the gut microbiota to prevent atherosclerosis. Indeed, non-lethal inhibition of TMA production by the gut microbiota with the use of 3,3-dimethyl-1-butanol, a structural analogue of choline, prevented endogenous macrophage foam cell formation and atherosclerotic lesion development in a mouse model. [53]

In response to a high-fat diet, the gut microbiota produces endotoxins which induce vascular inflammation and metabolic disorder via CD14. [54, 55•, 56] Endotoxins also engage toll-like receptor-4 and activate signalling pathways leading to the expression of inflammatory cytokines and left ventricular (LV) dysfunction. [57]

Previous studies suggested that the gut microbiota regulates the host's metabolic function. [58] When the faeces of obese mice were transplanted to germ-free mice, their total body fat was significantly increased compared with germ-free mice that received a faecal transplant from lean mice, [58] indicating that the microbiome from obese mice has an exaggerated capacity to harvest energy from the diet. Although the interpretation of this analysis is currently under discussion, [59] interest in the impact of the gut microbiome on atherosclerotic disease is certainly growing and further studies are clearly warranted.

Hypertension

Hypertension is the most common, preventable cause of CVD, where 31% of the world's adults have hypertension and, of these, only 13.8% are adequately controlled. [60] The overall SNS activity in some subjects with neurogenic hypertension is known to be higher than that in normotensive subjects. [61] On the other hand, in obesity-related hypertension, one of the most common forms of essential hypertension; the regional cardiac noradrenaline spillover is reduced with being 40–50% of that of healthy lean subjects. [62, 63] The chronically elevated SNS outflow to the peripheral organs, such as heart, arteries, and kidneys, increases LV workload that can result in impaired LV relaxation, left atrial enlargement, increased LV filling pressure, and a higher incidence of arrhythmias, particularly atrial fibrillation, all leading to heart failure.

We now mark 5 years since the first seminal studies in the field that showed that [1] animal models (angiotensin II (Ang II), spontaneously hypertensive rats (SHR)) and hypertensive subjects have a different gut microbiome composition compared with normotensive counterparts [11]; Ang II–induced vascular inflammation is attenuated in germ-free mice compared with conventionally raised mice, suggesting that the gut microbiota is important for the development of hypertension [64]; the gut of pre-hypertensive SHR has higher fibrosis, and lower gut epithelial integrity [5]; and importantly, whether directly or indirectly, the gut microbiota of hypertensive subjects indeed increases blood pressure. [65] In this study, faecal samples from two hypertensive and one normotensive subjects were transplanted into germ-free animals. Mice that received the faecal transplant from hypertensive subjects went

on to develop higher blood pressure compared with those that received a faecal transplant from the normotensive subject. [65] In addition, orally administrated minocycline reduced gut dysbiosis and also attenuated the hypertension of Ang II animals. [66] These results implicated the gut microbiota in the development and maintenance of hypertension.

Our seminal study demonstrated that prebiotic fibre acts through the gut microbiota to increase acetate-producing bacteria and acetate levels to lower blood pressure. [10•] This study demonstrated the importance of dietary intake of fibre and supplementation with SCFA to lower blood pressure and reduce cardiac remodelling through the modification of the renal and cardiac transcriptome. Our more recent findings support that lack of prebiotic fibre not only is a risk factor for the development of hypertension but also leads to the development of a hypertensinogenic microbiota that can be transferred to germ-free mice. [67] Lack of prebiotic fibre leads to high total peripheral resistance, lower sodium to potassium excretion in the urine, and lower levels of the catecholamine L-DOPA, while high levels of fibre result in methylome-wide changes that increase differentiation and number of anti-inflammatory T regulatory cells. [67] Further evidence from us and others now supports that other SCFAs such as butyrate and propionate can also lower blood pressure, [67–69] but acetate seems to have the biggest blood pressure–lowering effect of the three main SCFAs. Receptors for SCFAs, such as the G protein–coupled receptor GPR41, are abundantly expressed in the sympathetic ganglia in mouse and humans, [70] but overall these receptors are especially found in immune cells. [67] There is evidence, however, that GPR41 directly regulates sympathetic nervous activity and, thereby, controls body energy expenditure in maintaining metabolic homeostasis. [70, 71] Another possible receptor for SCFAs (particularly propionate) is the olfactory receptor 78 (Olf78) which modulates renin secretion in the kidney. [72] Our newest study addressed some of the lack of evidence for the role of other known SCFA receptors in blood pressure regulation, such as GPR43 and GPR109A. [67] Indeed, double GPR43/109A knockout mice had the highest degree of cardiac dysfunction compared with wild-type as well as single knockout models for GPR41, GPR43, and GPR109A. [67]

Heart Failure

Evidence reviewed above supports a direct or indirect role of the gut microbiota and their metabolites in the development of atherosclerosis, obesity, hypertension, and kidney disease, all of which are risk factors for heart failure. Indeed, transcriptome-wide changes in the heart itself can be a consequence of changes in the gut microbiota and its metabolites. [10•] Similar microbiome imbalance was observed in human obese and diabetic subjects. [58] The abundance of *Bacteroides* improved after weight loss due to dietary restriction of fat and carbohydrates. [73] Hyperabsorption of nutrient is considered one of the potential mechanisms that gut microbiome contributes to adiposity and the nutrient load is a key variable that influences the gut bacterial community structure. [58] These studies suggest that the gut microbiome is associated with both sides of the energy balance equation through the regulation of host genes that control adiposity. [74, 75]

It is no surprise that, independently of previous risk factors (which on their own are associated with dysbiosis), during heart failure lower levels of oxygen reach the gut and can impair the gut epithelial barrier. [76] Patients with heart failure have an increased quantity of pathogenic faecal bacteria and higher density of bacteria adhered to colon mucosa, which is associated with intestinal permeability. [77] Indeed, intestinal congestion is particularly common in heart failure. [78] Pro-inflammatory activation induced by intestinal congestion has been implicated as a potential mechanism of cardiac cachexia. [79]

The gut microbiota is known to prime the physiological structure of lymphoid tissue by driving the functional interactions of all elements of the adaptive immune system from neonatal age, [80] and is implicated in the leakiness of the intestinal barrier. [81] Moreover, the gut microbiota modifies the polarization of T cell subsets and natural killer T cells, which are likely to contribute to intestinal barrier dysfunction. [8] High serum endotoxin and cytokine levels (which can be reduced by diuretics) [82] and high endotoxin and lipopolysaccharide (LPS) levels have been reported both in congestive heart failure and end-stage renal failure. [83] These suggest that changes in the intestinal barrier induced by heart failure may favour the increased translocation of gut microbiota and the microbial products from the intestinal lumen into the systemic circulation, a process that could account for the persistent systemic inflammation in heart failure patients.

Increased SNS in addition to reduced vagal nerve tone is a known pathophysiology of heart failure and is also common during gut dysbiosis. [84] Autonomic disturbances, particularly increased renal sympathetic nervous activity and reduced cardiac vagal tone have been a key feature and treatment target of cardiorenal syndrome. Impaired vagal nerve activity of the heart has been observed in heart failure and several studies tested the efficacy of vagal nerve stimulation but a benefit has yet to be established. [84, 85] However, given the pathophysiology of inflammation, vascular atherosclerosis, and hypertension in heart failure, it would be interesting to hypothesize decreased vagal efferent tone to the gut as a potential treatment target.

Future Directions

The gut microbiota can increase immune reaction and cause failure of immune regulation in various organs through

intestinal barrier damage and molecular mimicry. We are still in the early stages of fully comprehending all the genes, metabolites, and proteins of the microbiota, as well as related neuro-enteroendocrine agents that associate complex interactions between the gut and CVD. Further research is clearly warranted to reveal the pathogenic role of the gut microbiota in CVD risk factors and heart failure, and to establish therapeutic interventions that ameliorate dysbiosis. Future research should be aimed at identifying specific phenotypes within heart failure that are closely related to gut dysbiosis and would potentially benefit from treating dysbiosis.

Conclusions

Until the past decade, the gut microbiota was neglected by cardiovascular science as a source of triggers for CVD and heart failure. Based on the current state of the literature, it can be concluded that manipulating the gut microbiota, either by the use of prebiotics or postbiotics, has the potential for the prevention and treatment of heart failure and its associated risk factors. Pre- and postbiotics have the therapeutic potential to modify immune system deregulation, enteroendocrine disruptions, and neurohormonal activation in patients with CVD and to improve cardiovascular outcomes.

Funding Information Y. Sata was supported by a National Heart Foundation Postdoctoral Fellowship and is now supported by the Baker Institute's Emerging Leader Fellowship; F.Z. Marques is supported by a National Heart Foundation Future Leader Fellowship and Vanguard Grants, and a National Health and Medical Research Council of Australia Project Grant; and D.M. Kaye is supported by a National Health and Medical Research Council of Australia Program Grant and Fellowship. The Baker Heart and Diabetes Institute is supported in part by the Victorian Government's Operational Infrastructure Support Program.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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