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Review Article

Associations between the gut microbiome, gut microbiology and heart failure: Current understanding and future directions

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ABSTRACT

The role of the gut microbiome in pathophysiology, prognostication and clinical management of heart failure (HF) patients is of great clinical and research interest. Both preclinical and clinical studies have shown promising results, and the gut microbiome has been implicated in other cardiovascular conditions that are risk factors for HF. There is an increasing interest in the use of biological compounds produced as biomarkers for prognostication as well as exploration of therapeutic options targeting the various markers and pathways from the gut microbiome that are implicated in HF. However, study variations exist, and targeted research for individual putative biomarkers is necessary. There is also limited evidence pertaining to decompensated HF in particular. In this review, we synthesize current understandings around pathophysiology, prognostication and clinical management of heart failure (HF) patients, and also provide an outline of potential areas of future research and scientific advances.

1. Introduction

The gut microbiome refers to the collection of microorganisms such as bacteria, archaea and eukarya found within the gastrointestinal tract and their environment, including molecular metabolites and surroundings, whereas the gut microbiota refers to all living microorganisms within this environment [1,2]. It is an area of active research, with an increasing understanding of its role in cardiovascular disease (CVD) [3,4]. It has many functions, including protective immune functions and metabolic functions related to drug absorption, and is now increasingly viewed as an endocrine organ, due to its ability to secrete biologically active compounds into the bloodstream, which can influence distant locations within the body [3]. Notably, the gut microbiome is not stagnant, and can be influenced by lifestyle, diet and medications [3,5]. In humans, the gut microbiome is primarily composed of *Bacterioides, Firmicutes, Actinobacteria, Proteobacteria* and *Verrucomicrobia*, with the former two being the most common [6]. Variations exist in the proportions of different microflora based on individual factors, with dysbiosis thought to play a role in the pathogenesis and prognosis of disease processes, including heart failure (HF). Both dysbiosis and changes in bacterial metabolite levels are thought to contribute to HF development, pathogenesis and prognosis, though the mechanisms by which and timeframe in which this may occur are yet to be clearly elucidated [3,6]. Indeed, chronic HF patients have been shown to have intestinal growth of other pathogenic microorganisms such as *Candida, Campylobacter, Shigella* and *Yersinia* [7,8]. Overall, HF is a complex disease entity, with a consensus definition as follows: "a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion" [9]. It can be classified into further subtypes based on left ventricular ejection fraction (LVEF), including HF with reduced ejection fraction (HFrEF), where LVEF $\leq$40 %, and HF with preserved ejection fraction (HFpEF), where LVEF $\geq$50 %, among others [9,10]. This literature review will explore important markers and pathways implicated in gut microbiota and host interactions, synthesize current understanding

Abbreviations: CVD, cardiovascular disease; HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TMA, trimethylamine; TMAO, trimethylamine N-oxide; BAs, bile acids; TAC, transverse aortic constriction; MI, myocardial infarction; CR, cardiac remodeling; FMT, fecal microbial transplantation; DMB, 3,3-dimethyl-1-butanol; FMC, fluoromethylcholine; IMC, iodomethylcholine; RDN, renal denervation; Coronavirus Disease 2019, COVID-19; CO, cardiac output; TMALIs, trimethylamine lyase inhibitors.

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of how these are influenced in HF, with a particular focus on acute decompensated HF, and briefly outline potential therapeutic options for chronic HF and areas of further research.

2. Methods

Databases including PubMed/Medline and Google Scholar were searched using combinations of keywords including "heart failure", "chronic heart failure", "decompensated heart failure", "gut microbiome" and "gut microbiota". Search keywords were later expanded to include specific metabolites "TMAO", "SCFAs" and "BAs", and a literature search undertaken for each individual topic area to summarize recent advances for each of these, prior to synthesis of evidence using the SPIDER framework, containing sample (HF patients), phenomenon of interest (gut microbiome activity), design (both preclinical and clinical evidence), evaluation (changes in gut microbiome activity during HF; therapeutic options; gaps in existing literature) and research type (qualitative and quantitative measures) [11]. Original research articles, review articles, perspective articles, systematic reviews and meta-analyses were all considered, as were references thereof. No date ranges were applied, and only English language articles were considered.

3. Physiological Pathways

The gut microbiota is thought to interact with hosts through metabolism-independent and metabolite-driven pathways. The former can include bacterial cell wall products such as peptidoglycan, and lipopolysaccharide (LPS) and the latter can include short-chain fatty acids (SCFAs), trimethylamine (TMA)/Trimethylamine N-oxide (TMAO), and bile acids (BAs) [3,6].

SCFAs are generally produced from saccharolytic and proteolytic catabolic pathways involving intestinal flora, with the common products being acetate, propionate and butyrate. These have important regulatory roles in the integrity of the intestinal barrier, with in-vitro evidence suggesting that they may even be able to contribute to repair of intestinal barrier function. This regulatory role is thought to be related to their role in maintaining a chronic hypoxic state, which is necessary for gut barrier integrity. Additionally, it was recently shown that SCFAs can increase tight junction protein expression and mucin production in response to external stressors, in the form of chemotherapy, thus protecting barrier integrity [3,5,7,12–15]. TMAO is a breakdown product of L-carnitine, choline or phosphatidylcholine, found in foods such as red meat, which are converted to TMA by intestinal flora, which itself is subsequently converted to TMAO in the liver by proteins known as flavin-containing monooxygenases (FMOs) [3,4,6,16]. Notably, phosphatidylcholine is also a major component of bile, and thus TMAO production occurs even in those who do not consume red meat, meaning that strategies aimed at targeting this pathway are also of clinical and research interest along with dietary modifications [3,6,17]. BAs are a constituent of bile, which is produced by the hepatic breakdown of cholesterol. Primary BAs are those produced by the liver, and enter the

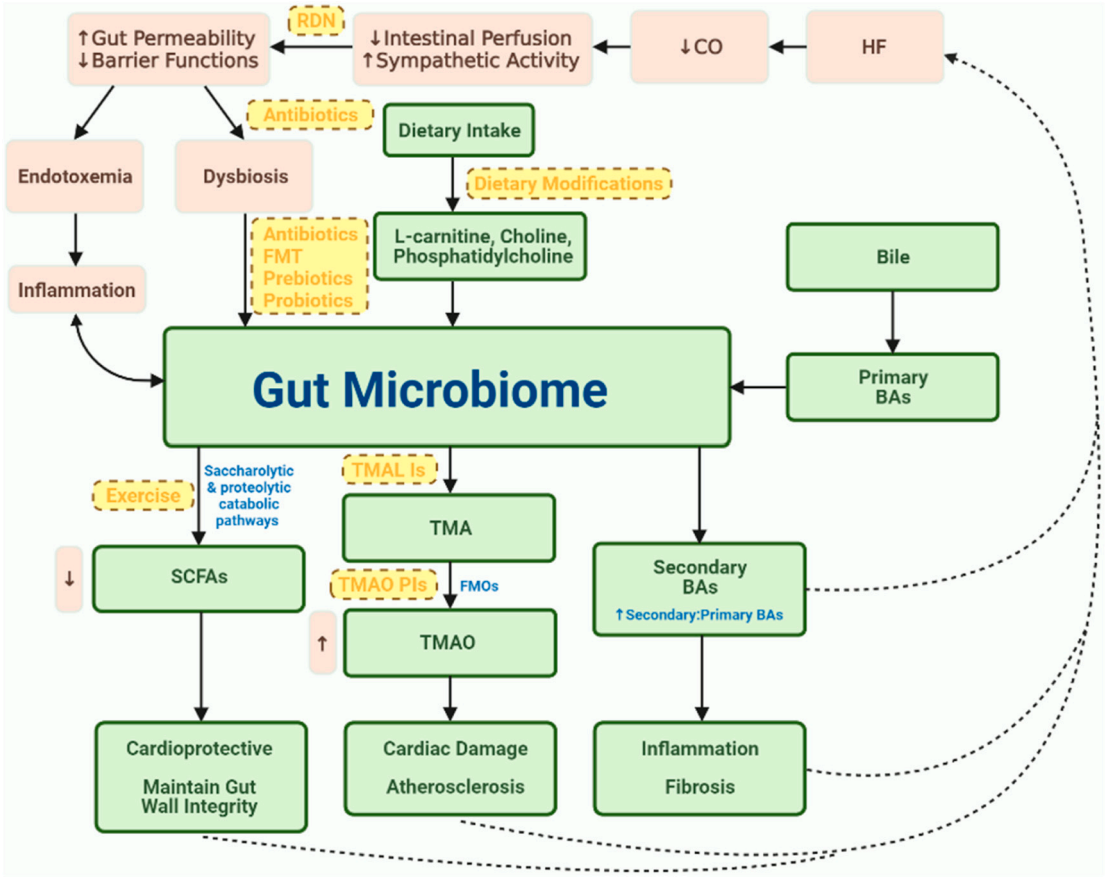

Fig. 1. Diagram summarizing known normal physiological processes (green, solid outline), with impacts of heart failure (HF) (red, no outline) and sites of action of potential therapeutic targets (yellow, dotted outline). Alterations or dysfunction in normal physiological processes are thought to have a possible role in HF development, though further research is needed to fully elucidate this (indicated using dotted lines). Abbreviations: CO = Cardiac Output, FMT = fecal microbiota transplantation; SCFAs = Short Chain Fatty Acids; TMA = trimethylamine; TMALIs = trimethylamine lyase inhibitors; TMAO = Trimethylamine N-oxide; PIs = Pathway Inhibitors; BAs = Bile Acids; RDN = Renal Denervation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

intestines post-prandially with bile. Breakdown from primary BAs to secondary is performed by colonic gut microorganisms in the intestines. As such, BAs have a key role in the breakdown of cholesterol and subsequent mitigation of atherosclerotic effects. BAs are also known to have signaling roles, particularly after entering the enterohepatic circulation [5–7,18,19]. In physiological conditions, these pathways and metabolites are important in maintaining health and balance, but changes in the proportions of these metabolites and microbes producing them can impact health and wellbeing, and certain changes have been implicated in HF (Fig. 1) [6,7]. Gut dysbiosis is also implicated in other cardiovascular conditions such as diabetes and atherosclerosis, which are themselves risk factors for HF development [20–23].

The role of the sympathetic nervous system should also be noted, with sympathetic compensatory mechanisms restoring cardiac function to baseline during acute situations. Such mechanisms include activation of the renin-angiotensin-aldosterone system and reductions in peripheral blood flow. Prolonged overactive sympathetic compensation causes HF [24,25]. The gut microbiome may be able to modulate this sympathetic activity, with a recent mouse model study showing that microbiota depletion resulted in increased expression of c-FOS, a marker of neuronal activity, and colonization of mice with SCFA-producing bacteria suppressed c-FOS in gut sympathetic ganglia. Additionally, it was also found that brainstem sensory nuclei were activated during depletion, along with efferent sympathetic premotor glutamatergic neurons, suggesting the presence of a bidirectional circuit [26]. Additionally, recent evidence suggests that TMAO may also impact sympathetic activity, with inhibition of TMAO production associated with improvement in sympathetic excitation in rats fed a high salt diet [27]. In light of this, gut dysbiosis leading to altered levels of metabolites such as TMAO, SCFAs and BAs may not only have local intestinal actions contributing to HF development, but may also cause increased sympathetic activation and subsequent end-organ impacts that may play a role in both HF development and development of HF risk factors such as hypertension [28,29]. This putative interaction between the sympathetic nervous system and gut microbiota is further supported by a recent work by Nemet et al. who showed that phenylacetylglutamine, a gut microbiota derived metabolite, was able to mediate and foster platelet function and thrombosis via α2A, α2B and β2 adrenergic receptors. Additionally, as adrenergic receptor signaling is implicated in HF development, this further suggests that the gut microbiome may influence HF pathogenesis through sympathetic mechanisms [24,30,31].

4. Changes in Heart Failure

In HF, reduced cardiac output can lead to intestinal hypoperfusion, also contributed to by circulatory congestion. Increased sympathetic tone, initially compensatory but later overactive, is also thought to contribute via vasoconstriction. Additionally, preclinical studies have demonstrated downstream inflammatory impacts which can accentuate atherosclerosis and fibrosis, and subsequent HF progression [8,32–35]. Bowel wall oedema is also seen, with these factors thought to cause hypoxia in the intestine; indeed, intestinal oedema has been previously associated with poorer outcomes in hospitalized HF patients [4–6,36]. This results in reduced mucosal pH and subsequently, impacts carrier-mediated transport within the gut, which has the dual effect of increased gut permeability and reduced barrier functions. Subsequent to this, there can be bacterial translocation into the circulation, and endotoxemia, which can enhance inflammation in HF patients [4–6,12]. This is supported by studies showing that decompensated HF patients have higher blood LPS levels [7,37–39], and observational studies showing that chronic HF patients have increased intestinal wall thickness, insufficiency and permeability [4,6,8,12,40]. Recent preclinical evidence from Boccella et al., who used a murine transverse aortic constriction (TAC) model of pressure-overload HF, provides mechanistic support to the latter. The TAC model can mimic a more gradual time course of HF development than other preclinical models. It was shown that TAC caused intestinal barrier dysfunction and significantly increased serum LPS and cytokine levels, as compared to sham-operated controls [41,42].

Intestinal hypoperfusion is also associated with dysbiosis, with studies showing increased pathogenic bacterial colonization such as *Shigella* in decompensated HF patients as compared to compensated HF patients, in a relatively rapid timeframe [43]. Increased sympathetic drive also contributes, having been shown to precede and be associated with gut dysbiosis and inflammation [44]. Additionally, HF patients have decreased levels of SCFA-producing bacteria and increased TMAO-producing bacteria, along with reduced overall microbial diversity [3,6,7,45]. Evidence suggests that these metabolites can be absorbed into the intestinal circulation and resultantly impact distal organs, including the heart, thus contributing mechanistically to HF prognosis, as well as having potential to act as biomarkers (Fig. 1) [12].

4.1. Trimethylamine N-Oxide (TMAO)

Animal models have shown that rodents with increased dietary TMAO and TMAO treatment exhibit structural changes including fibrosis and chamber dilation, and significantly worse cardiac function, with reduced TMAO showing beneficial effects [7,46,47]. Whilst neither of these studies directly manipulated the gut microbiome to produce TMAO, TMAO is a known metabolite of various gut bacteria and thus it is plausible that dysbiosis leading to increased TMAO would cause these impacts. Additionally, TMAO has also been reported to have multiorgan inflammatory effects, with reduced levels associated with reduced inflammation in rodent models, which can contribute to HF progression, in particular due to associations of elevated plasma TMAO with impaired renal function [21,48]. These results suggest strongly that TMAO has mechanistic effects, although studies are yet to clearly elucidate human pathogenesis [7]. TMAO has also been associated with more advanced left ventricular diastolic dysfunction and has utility in predicting poorer long-term outcomes in chronic systolic HF patients [12,49]. It has also been implicated in other atherosclerotic and CVD, which are themselves associated with myocardial ischemia and infarction [21,50], as well as conditions such as diabetes [21], which are associated with increased risk of HF development [20,21]. Indeed, TMAO has been associated with increased platelet responsiveness and activation, and was able to predict thrombotic event risk [51]. Nevertheless, there is a paucity of studies considering acute or decompensated HF; a recent 2020 meta-analysis reported that TMAO could predict poor prognoses in HF patients, but only one of the included studies considered acute HF [52,53]. Two more recent 2021 studies of acute HF patients reported predictive value for longer-term outcomes [54] and potential intestinal overgrowth [55], respectively. A 2022 meta-analysis similarly reported that elevated TMAO was significantly associated with major adverse cardiac events and all-cause mortality; this meta-analysis included ten studies, of which only three reported on cohorts of acute HF patients. Subgroup analysis by acute and chronic HF was performed for the latter outcome, all-cause mortality, and significance of the results maintained. However, this study was not able to account for dose-response relationship between TMAO levels and poor prognosis due to few included studies providing relevant data [56]. As such, further research is warranted to clarify this association and clinical implications thereof.

4.2. Short Chain Fatty Acids (SCFAs)

Common SCFAs include acetate, propionate and butyrate; these are generally found in the colon, but can also be found systemically, with various resultant physiological impacts [7]. Previous studies have shown a reduction of SCFA-producing bacteria in HF patients, such as *Faecalibacterium prausnitzii*, and bacteria from the *Lachnospiracea* and *Ruminococcacea* families, known to contribute significantly to butyrate production [7,57–59]. This suggests that SCFA-producing bacteria may

have cardioprotective effects. Indeed, considering other CVD, reductions in butyrate-producing microbial species have been previously associated with an increased risk of atherosclerotic lesion development [60]. Whilst there are a number of purported implications and links of SCFAs with CVD, with preclinical studies showing that increased dietary SCFAs improve cardiac function, these links are yet to be clearly elucidated in the context of HF [7,12]. The current state of evidence around their role in HF development is summarized in the following paragraph.

Specifically, SCFAs have been shown to have immune mediatory impacts, with subsequent impacts on cardiac structure and function, particularly via enhancement of anti-inflammatory regulatory T cell pathways [4,6]. Additionally, they have also been shown to have modulatory impacts on blood pressure, which could impact HF development, though further research is required to clarify this putative association [6,12]. Importantly, SCFAs, particularly butyrate, are thought to have a role in maintaining integrity of the gut barrier. This is via promotion of intestinal epithelial cell differentiation, reparation of damaged mucosa, tight junction protein expression, mucus generation and mediation of inflammation caused by circulating exogenous substances, and potentially a response to external stressors to reverse changes that occur [6,7,14,15]. Additionally, in the colon, butyrate is thought to activate hypoxia inducible factor to assist in maintenance of the gut barrier, as the physiologic state of this region is relative hypoxia [12,14]. As such, hypotheses pertaining to reductions in SCFAs having a role in HF are corroborated by observed increases in gut permeability in HF patients [8,40,57]. As with TMAO, there is a gap in the literature in the context of decompensated HF patients with, to our knowledge, no studies exploring the role of SCFAs in outcomes for this group.

4.3. Bile Acids (BAs)

It has been previously shown that BAs have a role in signaling upon entering the systemic circulation, and BA receptors have been found in cardiomyocytes, suggesting that they may influence cardiovascular function [5,7,57]. Secondary BAs are thought to have major roles, and it was recently shown that an increased ratio of secondary to primary BAs in chronic HF patients predicted reduced overall survival in unadjusted analyses [5,57,61]. Additionally, BAs are also thought to influence inflammation and fibrosis, along with intestinal barrier integrity, hence having another potential role in HF pathophysiology [7]. The G protein-coupled receptor TGR5 and nuclear receptor farnesyl X receptor (FXR) have both been implicated in mediating actions of BAs. TGR5 is thought to be cardioprotective, but there is controversy around the role of FXR, with further studies required to elucidate this [6,7,37]. Gut dysbiosis and its subsequent impacts on BAs and their levels may also have indirect contributions to HF development, due to the important role BAs play in cholesterol metabolism and subsequent excretion [18]. The role of BAs in decompensated HF is also not clear and warrants further study.

5. Therapeutic Options

Therapeutic guidelines for HF have recently been published, with comprehensive recommendations for management of HF and its various subtypes. Both non-pharmacological and pharmacological measures are recommended, stratified as per the new the Universal Definition and Classification of Heart Failure, with strong class 1 evidence for most disease phenotypes, barring pharmacological agents targeted at HFpEF specifically [10]. However, considering previous results that chronic HF patients with high TMAO levels had worse outcomes and TMAO levels did not respond well to guideline-based therapies, and that adding TMAO to a model with B-type natriuretic peptide improved prognosis, further research related to therapeutic mechanisms targeting manipulation of the gut microbiome may be useful [62]. Despite this, there is no mention of such therapeutic options, owing to these being currently in their infancy; though some therapeutic options have been implemented for treatment of other clinical conditions, their use in HF is currently in either hypothetical or experimental stages, with further validation necessary. These also include non-pharmacological measures such as alterations in diet, metabolite levels and microbial flora. However, the majority of these are focused on chronic HF as opposed to acute (Fig. 1) [3,63].

5.1. Lifestyle Modifications

Reducing dietary red meat lowers the intake of TMAO precursors, with patients receiving a Mediterranean diet shown to have reduced CVD and mortality risk [3,6,17]. Indeed, it has been shown in clinical studies that changing to a red meat free diet can cause rapid reductions in plasma TMAO levels [50]. Additionally, high-fiber diets have been shown to prevent HF development in preclinical studies, thought to be related to an increased production of the SCFA acetate, and subsequent beneficial cardioprotective and gut barrier maintenance effects [6,7,12,64]. A western diet low in fiber and rich in saturated fat has been shown to increase intestinal permeability and subsequently increase circulating LPS and endotoxaemia [7]. Notably, whilst such dietary modifications have been shown to have beneficial impacts on cardiac function and HF biomarker levels, impacts of other concomitant lifestyle interventions are unclear, and hence further studies exploring the impact of dietary interventions in conjunction with existing lifestyle strategies in HF patients is necessary [6].

Exercise is also emerging as a modulator of the gut microbiota and has subsequent beneficial impacts on cardiac function, particularly being associated with increased levels of the SCFA butyrate [4]. Addressing sleep fragmentation, commonly reported in HF patients, has also been suggested as having therapeutic potential, though a recent preclinical mouse model study showed that whilst inducing sleep fragmentation and HF in the mice individually resulted in gut microbiome alterations, when both conditions were induced concomitantly there was no additional effect, and hence continuing research is necessary to further elucidate any links between sleep, gut microbiome alterations, and HF development and prognosis [65,66].

5.2. Antibiotics

Preclinical studies have shown a role for antibiotic therapy in HF treatment, which could modify the composition of the intestinal microbiota, but there is still a lack of clarity in human patients [7]. Another proposed reason for beneficial impacts of antibiotics is reduced bacterial translocation, and thus reduced systemic inflammation, but this has not been translated to improved clinical outcomes [6,57]. Additionally, previous studies have shown reduced plasma TMAO levels with antibiotic use, which rebounded after discontinuation thereof [21,67]. However, the Targeting Gut Microbiota to Treat Heart Failure (GutHeart) randomized controlled trial (RCT), which investigated the effect of the antibiotic rifaximin and the prebiotic *Saccharomyces boulardii* on LVEF and HF biomarkers relative to patients receiving standards of care only, showed no significant differences between groups [68]. Hence, in light of these variable results, further research is critical, especially considering the potential impact on beneficial gut bacteria viability that antibiotic use can have, which could cause overgrowth of harmful bacteria and contribute to antibiotic resistance risk, both of which could further complicate patient management. However, in the present, a personalized approach is necessary to ensure benefits of antibiotic use outweigh the risks for each patient [4,12,21,69].

5.3. Prebiotics and Probiotics

Prebiotics refer to food substrates able to promote growth of certain beneficial microorganisms [7]. Putative effective prebiotics may have benefits through actions at various points in the physiological pathways by which the gut microbiome and its metabolites may influence HF progression. They include various substances that can promote the

fermentation of dietary fiber into SCFAs, beneficial due to their cardioprotective effects and contribution to gut barrier maintenance [70,71]. Another substance with purported benefits at other points in the pathway includes *Bifidobacterium animalis* subsp. *lactis* LKM512, which was recently shown to reduce fecal TMA concentration, abundance of TMA-producing bacteria and serum tumor necrosis factor alpha levels in probiotic group vs placebo group, hence potentially reducing TMAO-related HF progression [72]. Preclinical studies also indicate that there may be a beneficial role of oligosaccharides, including those that are food-derived, as prebiotics. They have been shown to promote SCFA-producing bacteria and reduce opportunistic pathogenic bacteria, and may also prevent hypertension and HF development [70,71]. To our knowledge, there are few human studies pertaining to hypertension and HF specifically, but a recent double blind RCT showed that fructo-oligosaccharides dosage was associated with significant positive changes in both diversity and abundance of SCFA-producing organisms, including *Faecalibacterium*, *Ruminococcus* and *Oscillospira* [73]. These have previously been shown to be beneficial to cardiac health [7,57]. Additionally, prebiotics have also been shown to potentially oppose negative effects of antibiotics by promoting diversity in the microbiome, though evidence regarding any potential concurrent use is lacking, with the GutHeart trial not investigating this [7,57,68].

Probiotics are live microorganisms introduced in a bid to restore a healthy balance of microflora [7]. These include *Lactobacillus planatrum 299v*, which has shown utility in preclinical studies, and *Saccharomyces boulardii*, which showed improved cardiac function in a cohort of chronic HF patients, albeit with a small sample size [7,74]. However, the GutHeart trial showed no significant effect of *Saccharomyces boulardii* treatment on HF biomarkers or LVEF relative to the other intervention (antibiotic use) and control groups [68]. Probiotic use is also of interest after myocardial infarction (MI), as adverse cardiac remodeling (CR) may result in HF development. Probiotic use may have benefits post-MI due to reduced inflammatory activity, which could contribute to improved CR, and improvements in cardiac risk factors such as hypertension, dyslipidemia and diabetes mellitus [75–77]. Indeed, a recent RCT by Moludi et al. showed that probiotic use in this context was associated with improvements in echocardiographic indices, albeit not significantly [75]. Hence, probiotic use could be useful in certain clinical contexts, but further research is necessary to ascertain their clinical utility and which clinical contexts they may be useful in, particularly considering reported risk of probiotics undergoing translocation into systemic circulation [6,57].

5.4. Fecal Microbiota Transplantation (FMT)

Aimed at transferring functional bacteria from healthy subjects to patients and thus altering gut microbiota composition [4], FMT has shown utility in refractory *Clostridioides difficile* infections and inflammatory bowel disease. However, the potential for use in HF patients is unclear, with, to our knowledge, no studies in HF patients to date [6,7,12,21,57]. Additionally, infection, endotoxin transfer and rejection risks must be considered [21].

5.5. TMAO Pathway Inhibitors

Considering the understanding of TMAO as having a role in cardiovascular function and HF, there is great interest in inhibiting TMAO or TMA production. Drugs have been developed for this, inhibiting various aspects of the pathway, including 3,3-dimethyl-1-butanol (DMB), which is a choline analogue, and hence prevents TMA synthesis, as well as fluoromethylcholine (FMC) and iodomethylcholine (IMC), which both inhibit the TMA generating cutC and cutD enzyme pair. Each of these drugs was found to reduceplasma TMAO levels and improve cardiovascular structural changes and function, with the cutC/cutD inhibitors also associated with reversals in platelet hyperreactivity [47,78]. Encouragingly, these drugs were not associated with systemic toxicity. However, evidence suggests that factors other those targeted by these drugs are associated with TMA production [79]. Hence, further understanding of the underlying drug pathways being targeted is necessary to drive further development of such drugs and understanding of efficacy [4,12,21,47,78,79]. Additionally, a personalized medicine approach which considers how individuals may produce and metabolize TMAO uniquely based on underlying factors is of great clinical interest [69]. It has also been recently shown that the cntA/B complex, a gene cluster involved in TMAO production, was positively correlated with TMAO levels in HF patients, particularly from the Escherichia and Klebsiella genera. As such, strategies for targeting dysbiosis may be of additional clinical value by facilitating reduced TMAO or causing TMAO inhibition [80].

5.6. Renal Denervation (RDN)

Recently, RDN has emerged as a potential treatment for HF, as it reduces global sympathetic tone and thus may address the role the sympathetic nervous system plays in HF pathophysiology and development [81]. It has previously been shown that RDN has benefit in treatment of hypertension, which can contribute to HF development [81,82], and was recently shown that RDN may be a safe and effective treatment for HF with preserved ejection fraction, with benefits appearing to be independent of blood pressure changes [81,83]. The relationship between RDN and the gut microbiome is of particular interest, with Guo et al. reporting that RDN was able to reverse abnormal gut microbiome changes in rats with chronic HF, with increased abundances of beneficial bacteria and reductions in harmful bacteria observed [84]. However, further preclinical and human studies are necessary to validate these preliminary findings, and better understand the mechanisms underlying these changes.

6. Conclusions and Future Directions

There is now an increased appreciation of the potential interrelation between the gut microbiome and CVD, including HF. However, further clarification of mechanistic roles of underlying metabolites and their potential as biomarkers is necessary, with TMAO being particularly promising in this regard. Further research into its prognostic capabilities is warranted, as well as studies looking at whether SCFAs and BAs can be used in this manner. If found to have prognostic value, such biomarkers could have a role in risk stratification in HF, with incorporation into nomograms along with other biomarkers that have been shown to have benefit, such as natriuretic peptides, potentially ameliorating their predictive value [85,86]. Indeed, using nomograms has been shown to have benefits in prognostication and readmission previously in chronic HF, which could benefit risk stratification for HF patients and thus guide treatment decisions [87]. Additionally, biomarker evidence of HF has recently been included in the new Universal Definition and Classification of Heart Failure, as part of the criteria for Stage B ‘pre-heart failure’, which refers to those without symptoms or signs but with any one of structural heart disease, abnormal cardiac function and elevated biomarkers, specifically natriuretic peptides or troponin [9]. As such, if the prognostic capability of TMAO, SCFAs and BAs as biomarkers was to be validated, these could potentially be incorporated into such definitions to further improve and guide risk stratification, considering that they have been implicated in HF pathophysiology. Additionally, as natriuretic peptides can also be elevated in disease conditions other than HF, such as chronic kidney disease or atrial fibrillation, the use of multiple biomarkers may facilitate an individualized approach to diagnosis and risk stratification [9,88,89]. However, there are variations in specific patterns of dysbiosis for each compound discussed, and previous studies have had marked variations in study populations and protocols [69]. As such, further targeted research pertaining to each of these putative biomarkers is warranted, with measurement of blood and urinary levels of particular relevance for potential future clinical uptake [21].

Previous research is also limited by a lack of clarity around the extent of diversity within the microbiome. Thus, further research with large sample sizes and comprising subgroup analyses of participants who have other factors that influence variability of the microbiome such as ethnicity, age, long-term medication and antibiotic use, and disease conditions such as diabetes and autoimmune conditions is critical, and may inform further understanding of the gut microbiome in physiological settings, along with how this may change from a pathophysiological point of view in HF [21,34,90]. Machine learning applications may be of relevance for this, considering the vast number of factors interacting with the gut microbiome and the high levels of diversity, and have been proposed in other contexts with similar high data volumes in order to ascertain clinically relevant relationships and patterns [34,91]. In fact, machine learning has previously been shown to have value in personalizing dietary advice provided to patients [57,92,93]. The role of comorbid conditions such as hypertension and atrial fibrillation must also be considered during this process, as these may influence treatment response due to the shared underpinnings these conditions are thought to have [81]. Additionally, the gut microbiome and metabolites have been implicated in graft survival and treatment response in HF patients requiring heart transplantation (HT). It has also been shown that TMAO levels remain elevated even after HT. As such, further research into the extent to which the gut microbiome impacts HT treatment response, and into the efficacy of combining HT with treatment strategies addressing gut microbiome changes is warranted [94,95].

There is a literature gap in acute decompensated HF patients, and further study of underlying mechanisms is particularly important in this group, along with larger scale studies to better understand prognostic utility [57]. During the Coronavirus Disease 2019 (COVID-19) pandemic, remote medicine and use of telemedicine to overcome staffing shortages and mandatory isolation periods has become increasingly necessary, and there has been a global shift towards telemedicine owing to the increased convenience and access to care it has provided. Additionally, there is increasing evidence of CVD in both paediatric and adult patients. As such, biomarkers that can predict outcomes and stratify risk for patients may assist with overcoming barriers related to physical examination imposed by telemedicine, and may also assist with resource allocation in such settings, as has previously been reported [96–100]. Additionally, it has been recently hypothesized that the gut microbiome may modulate COVID-19 infection response [101]. As such, a detailed understanding of underlying pathophysiological mechanisms of the metabolites outlined earlier could facilitate incorporation of these biomarkers into clinical decision making both during and beyond the COVID-19 pandemic, and influence development of therapeutic mechanisms, though further research and development of frameworks for a personalized approach to treatment seem to be critical for these metabolites to be clinically relevant as biomarkers [57,69].

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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