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Cardiovascular Disease and the Gut Microbiome

Introduction

Cardiovascular diseases (CVD) are a group of disorders that affect the heart and vasculature system, increasing the risk of death significantly. More than four out of five CVD deaths are due to heart attacks and strokes; one-third of these deaths occur prematurely in people under 70 years of age.[1] High blood pressure, high blood cholesterol, and smoking are key risk factors for developing heart disease.

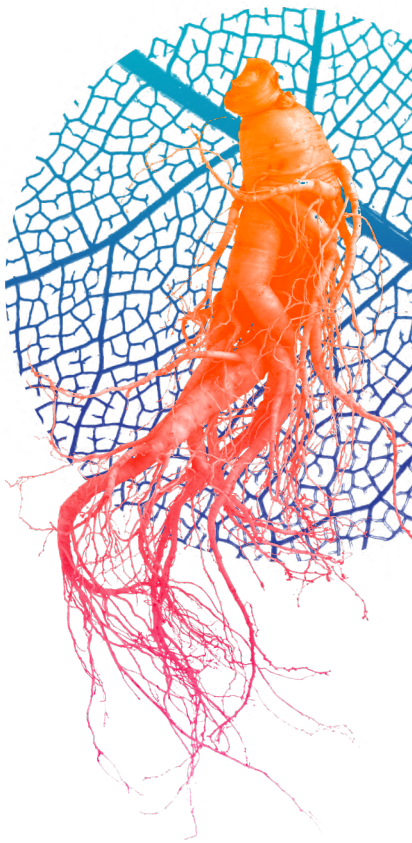
Epidemiology

Cardiovascular diseases are the leading cause of death globally, accounting for 17.9 million deaths which represent 32% of all deaths around the world.[2] Roughly 659,000 people in the U.S. die from heart disease each year – that's one in every four deaths. Some 18.2 million adults age 20 and older have coronary artery disease (about 6.7%), and about 805,000 people in the United States have a heart attack every year.[3]

Clinical Relevance

Cardiovascular disease may include any of the following:[2,4]

- **Coronary heart disease** – a disease of blood vessels in the heart muscle
- **Cerebrovascular disease** – a disease of blood vessels in the brain
- **Peripheral arterial disease** – a disease of blood vessels in the arms and legs
- **Rheumatic heart disease** – damage to the heart muscle and heart valves from rheumatic fever caused by streptococcal bacteria
- **Congenital heart disease** – malformations of the heart structure from birth
- **Deep vein thrombosis and pulmonary embolism** – blood clots in the leg veins, which can dislodge and move to the heart and lungs
- **Arrhythmia** – problem with the electrical conduction system of the heart, which can lead to abnormal heart rhythms or heart rates
- **Valve disease** – valve tightening or leaking
- **Heart failure** – compromised heart pumping/relaxing, leading to fluid buildup and shortness of breath
- **Aortic disease** – damage to the large blood vessel that directs blood from your heart to your brain and the rest of your body, such as dilatation or aneurysm
- **Pericardial disease** – problem with the lining of your heart, including pericarditis and pericardial effusion



[1] https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1

[2] https://www.who.int/en/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

[3] https://www.cdc.gov/heartdisease/facts.htm

[4] https://my.clevelandclinic.org/health/diseases/21493-cardiovascular-disease

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Risk Factors

The most important lifestyle risk factors for heart disease and stroke are unhealthy diet, physical inactivity, tobacco use, and overconsumption of alcohol. Hypertension, the most common form of CVD, is a major modifiable risk factor for many other CVDs, including acute coronary syndrome (angina and heart attack), cardiomyopathy, congestive heart failure, pulmonary hypertension, and stroke.[5,6]

Cardiovascular Disease and the Microbiome

Microbial dysbiosis has been linked to a host of local and systemic conditions, including cardiovascular disease.[7,8,9]

Dysbiosis of the gut microbiota can lead to a chronic upregulation of low-level inflammation via intestinal permeability and the translocation of bacteria and bacterial-derived metabolites known as pathogen-associated molecular patterns (PAMPS) into the systemic blood flow. Lipopolysaccharides (LPS), a toxin produced by gram-negative bacteria, are of particular concern in CVD. A mere two- to three-fold increase in LPS results in metabolic endotoxemia, a known risk factor for many CVDs.

PAMPs bind TLR4 (toll-like receptor 4), triggering the NF-kappa-beta pathway and resulting in systemic upregulation of low-grade inflammation.

Bacterial Metabolites and their Cardiovascular Effects	
PAMP/metabolite	Associated CVD[10,11,12]
LPS	CVD, atherosclerosis
TMAO (Trimethylamine N-oxide)	Endothelial dysfunction; exacerbated platelet reactivity; enhances thrombosis; affects lipid metabolism and inflammatory response
P-cresyl sulfate	CVD
Indoxyl sulfate	CVD

[5] https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2019/02/15/14/39/aha-2019-heart%20disease-and-stroke-statistics

[6] https://www.heart.org/en/news/2019/01/31/cardiovascular-diseases-affect-nearly-half-of-american%20adults-statistics-show

[7] https://www.ncbi.nlm.nih.gov/pubmed/31469291

[8] https://onlinelibrary.wiley.com/doi/full/10.1111/1440-1681.13250

[9] https://www.nature.com/articles/sj.bdj.2016.865

[10] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7442318/

[11] https://pubmed.ncbi.nlm.nih.gov/34414217/

[12] https://pubmed.ncbi.nlm.nih.gov/29020409/

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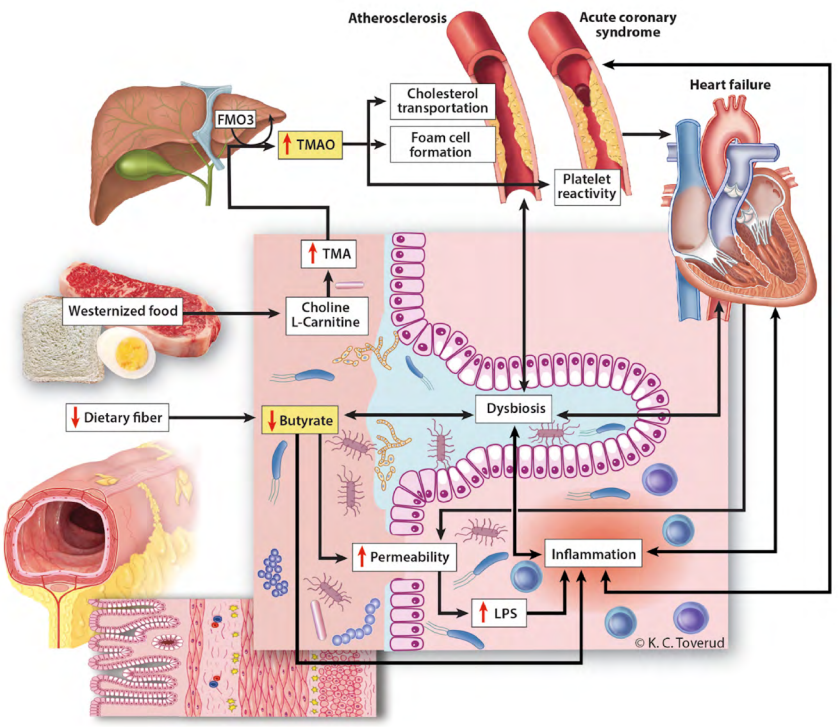

Figure 1. https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964%2820%2930024-4/fulltext

Dysbiosis is linked to atherosclerosis, ischemia, and stroke. Research shows that gut microbiome diversity is inversely associated with arterial stiffness, and that patients who experienced a stroke or ischemic attack as a consequence of atherosclerosis had fewer commensal or beneficial genera of microbes.[13]

Additionally, both TMAO (an amine oxide generated from choline, betaine, and carnitine by gut microbial metabolism) and LPS (an endotoxin found in the cell walls of certain gram-negative bacteria) make the vascular endothelium and plaque unstable and can promote thrombosis.[11] In an observational study, it was noted that circulating LPS concentrations were predictive of major adverse cardiac events in patients with atrial fibrillation.[14]

LPS binds to TLR4, which activates NF-κB and the NLRP3 inflammasome. This, in turn, leads to the overproduction of proinflammatory cytokines and adhesion molecules and contributes to atherosclerosis.[12]

Conversely, researchers noted that *Akkermansia muciniphila* (a keystone beneficial species) decreased intestinal permeability and lowered fecal and circulating LPS levels, which was associated with reduced aortic atherosclerosis independent of lipid metabolism.[14]

Balancing the microbiome provides healthcare providers with a critical therapeutic target to support patients in optimizing foundational health and cardiovascular health.

[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7996485/

[14] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7416843/

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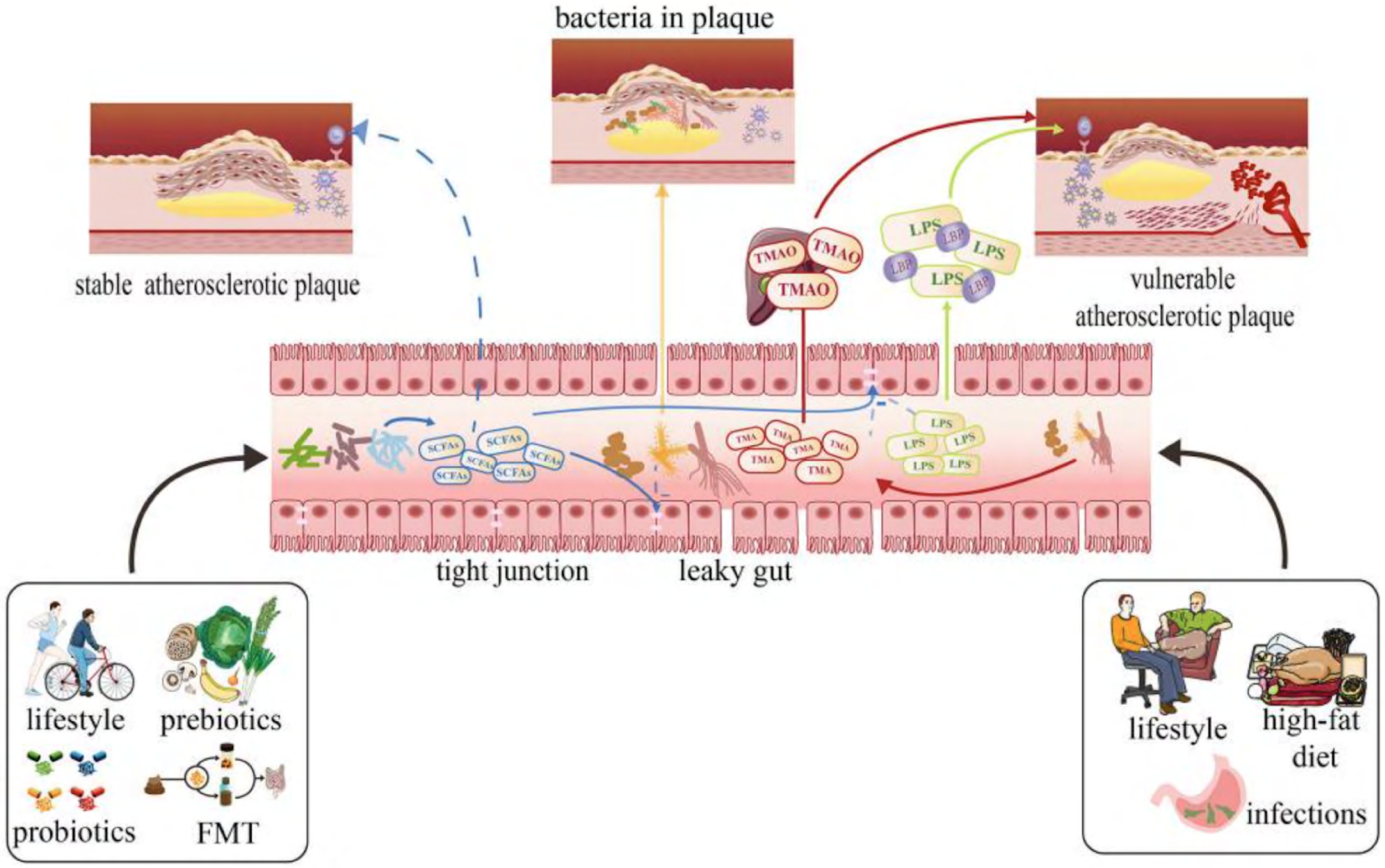

Figure 2. https://pubmed.ncbi.nlm.nih.gov/34414217/

Clinical Pearl #1 – Don't Forget the Mouth!

Pathogenic bacteria can be detected in atherosclerotic plaque of patients with periodontal disease and is well established as a risk factor for atherosclerosis and other CVD.[13] Periodontal disease is the most common inflammatory disease globally, affecting up to 77% of American adults over the age of 30.

The pathogenesis of oral dysbiosis is similar to gastrointestinal dysbiosis – promoting the release of pro-inflammatory cytokines and translocation of pathogens due to permeability of the gingival and periodontal epithelium. Treating periodontitis has been shown to reduce circulating inflammatory mediators such as C-reactive protein and interleukin 6, and may serve as a beneficial therapeutic strategy.

Clinical Pearl #2 – Include Fiber

Fiber-rich diets work in several ways to support cardiovascular health. High-fiber diets that include fruits, vegetables, beans, nuts, and seeds seem to effect change in the microbiome in as little as five days.[15]

Fiber has been shown to:

- Increase biodiversity and decrease non-favorable bacterial strains[16]
- Maintain or improve intestinal barrier function
- Inhibit cholesterol synthesis[13]
- Increase the production of short-chain fatty acids
- Decrease blood pressure
- Promote myocardial repair
- Reduce inflammation

Short-Chain Fatty Acids, commonly referred to as SCFAs, include acetate, propionate, and butyrate. They are produced via the metabolism of dietary fiber by bacteria and are protective through multiple pathways. **They nourish the intestinal epithelium and reduce inflammation in the gut and entire body, ultimately protecting the cardiovascular system.** Healthy microbial balance will naturally increase the prevalence of SCFAs while also reducing the production of damaging pro-inflammatory metabolites.

Clinical Pearl #3 – Get Patients to Move their Bodies

While exercise provides beneficial physiological effects, movement also has a significant impact on microbiome health. Aerobic and endurance exercise is correlated with increased diversity in the microbiome (specifically, keystone probiotic species *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*).[17,18] Encouraging patients to find a regular exercise routine that works for them will influence the microbiome and improve cardiovascular health.

Lifestyle Recommendations

- Support your treatment with simple yet effective lifestyle recommendations. Check out the recommendations contained in the Bioclear® Microbiome Detox Lifestyle Guide.
- Adopt a low-inflammation diet (Modified Paleo, Mediterranean, etc.), which includes a high intake of non-starchy vegetables.
- Keep pro-inflammatory fats to a minimum. Studies indicate that high-fat diets (in this case, soybean oil), especially when consumed alongside refined carbohydrates, may reduce protective SCFA production and increase concentrations of substances such as p-cresol, indole, arachidonic acid, and LPS in stools while increasing inflammatory markers in plasma.[19]
- Reduce overall caloric intake.
- Proactively work to lower stress.
- Increase exercise to support weight loss, blood sugar regulation, and cardiovascular health.

[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7117800/
[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7147654/
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7906424/
[18] https://pubmed.ncbi.nlm.nih.gov/37433843/
[19] https://pubmed.ncbi.nlm.nih.gov/30782617/

Therapeutic Plan Suggestions

General Dysbiosis Support		
CORE PROTOCOL – Bioclear™ Microbiome Detox Program		
Biocidin® Liquid or Capsules	Titrate to 15 drops 2x/day	Titrate to 2 capsules 2x/day
G.I. Detox™+	2 capsules at bedtime. 1 hour away from food, supplements, and medications. Temporarily increase dose to 2 capsules 2-3x/day if Herxheimer reaction observed/worsens.	
Proflora™ 4R	1 capsule any time	
G.I. InnerCalm™	1 stick pack mixed in water, 1-2 times daily, taken any time.	
ADDITIONAL SUPPORT		
Olivirex®	Titrate to 2 capsules 2x/day	
In the case of long-standing dysbiosis, testing for presence of pathogenic strains is highly recommended.		

Additional Therapeutics

Botanicals	Supplements
Hawthorn	Arterosil
Red Sage	CoQ10
Arjuna	EPA/DHA
Yarrow	Magnesium, Potassium
Motherwort	Vitamin K2
Ginkgo	Nicotinamide Riboside
Bilberry	L-arginine, L-citrulline
Hibiscus	Tocotrienols
Horse Chestnut	Resveratrol

Questions?

For clinical questions, email clinical@biocidin.com or call 800-775-4140, x3.