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Reviews

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The emerging oral–heart failure axis: Mechanistic plausibility, bidirectionality, and the limits of causal evidence. A state-of-the-art review

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Abstract

Heart failure (HF) is a systemic, multiorgan syndrome in which inflammation, oxidative stress, endothelial dysfunction, metabolic abnormalities, and frailty contribute to disease progression. Periodontitis may represent an additional extracardiac source of inflammatory and microbial exposure, whereas HF itself may promote deterioration of oral health through frailty, malnutrition, impaired self-care, and reduced access to dental treatment. This state-of-the-art review evaluates the emerging oral–HF axis, focusing on systemic inflammation, oxidative stress and mitochondrial dysfunction, endothelial and coronary microvascular dysfunction (CMD), and myocardial fibrosis and remodeling. Epidemiological studies support associations between adverse oral-health indicators and HF, particularly tooth loss and edentulism, but findings for periodontitis are less consistent and remain vulnerable to residual confounding, reverse causation, and heterogeneous exposure definitions. Experimental studies provide biological plausibility for inflammatory, oxidative, endothelial, and fibrotic pathways, yet direct human evidence linking periodontal inflammatory burden to CMD, myocardial remodeling, or HF progression remains limited. Mendelian randomization does not currently support a direct causal effect of periodontitis on HF, and periodontal treatment has not been shown to reduce HF hospitalization or mortality. The oral–HF axis should therefore be regarded as a biologically plausible, bidirectional framework in which periodontitis may act as a disease modifier rather than an established independent cause of HF.

Key words: periodontitis, inflammation, oxidative stress, endothelial dysfunction, heart failure

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Highlights

- Evidence supports a biologically plausible, bidirectional oral–heart failure axis, but does not establish periodontitis as an independent cause of heart failure.
- Tooth loss and edentulism show the most consistent epidemiological associations with incident heart failure, whereas findings for periodontitis remain less consistent.
- Inflammation, oxidative stress, endothelial dysfunction, coronary microvascular dysfunction, and myocardial fibrosis provide plausible mechanisms, but direct human evidence remains limited.
- Mendelian randomization does not support a direct causal effect of periodontitis on heart failure, and no completed heart failure-specific trial has established reductions in hospitalization or mortality after periodontal treatment.
- Periodontal assessment and appropriate treatment may form part of comprehensive care in patients with heart failure, but periodontal therapy cannot currently be considered heart failure-modifying treatment.

Introduction

Heart failure (HF) remains a major clinical problem, affecting more than 64 million people worldwide and contributing substantially to hospitalization, disability, and premature mortality.[1] Despite major progress in pharmacological and device-based treatment, its clinical course is strongly influenced by age, comorbidities, nutritional status, frailty, and dysfunction of organs outside the cardiovascular system.[2,3] This has broadened the view of HF beyond cardiac pump failure and increased interest in extracardiac factors that may contribute to disease susceptibility and progression.

One potential source of systemic inflammatory exposure is the oral cavity.[4–6] It contains a complex microbial community that continuously interacts with the host immune system. Disruption of periodontal homeostasis may promote local inflammation and provide a source of microbial products, inflammatory mediators, and transient bacteremia.[7,8] Periodontitis is a dysbiosis-associated chronic inflammatory disease characterized by progressive destruction of the tooth-supporting tissues, with clinical attachment loss, alveolar bone loss, periodontal pocketing, and gingival bleeding.[9] It should not be treated as equivalent to tooth loss, which is a cumulative endpoint with several possible causes, or to impaired mastication, swallowing dysfunction, and the broader construct of oral frailty. Marked tooth loss remains common among older adults despite improvements in population-level tooth retention and is associated with age, sex, education, and place of residence.[10]

Periodontal disease has been associated with systemic immune activation, endothelial dysfunction, altered redox regulation, and changes in host inflammatory signaling.[7,8,11] These mechanisms are well established in the wider periodontal–cardiovascular literature and provide biological grounds for considering an oral–HF axis. Their relevance to HF, however, is less certain. Most available evidence is observational, and mechanistic plausibility does not demonstrate that periodontal inflammation independently contributes to HF development or progression.[12]

The question may be particularly relevant in heart failure with preserved ejection fraction (HFpEF), where aging, multimorbidity, vascular dysfunction, and systemic inflammatory activation have a prominent role in disease biology.[2,13–15] Periodontitis could represent an additional inflammatory exposure in this setting, but this possibility remains hypothetical. The available literature does not establish an independent periodontal contribution to HFpEF, and mechanisms demonstrated in atherosclerotic cardiovascular disease (CVD) cannot be directly transferred to HF.

Shared risk factors further complicate interpretation. Aging, diabetes mellitus, obesity, chronic kidney disease, smoking, socioeconomic disadvantage, and access to healthcare are associated with both poor oral health and CVD.[16–18] Oral disorders may therefore act as markers of accumulated comorbidity and social vulnerability rather than direct determinants of HF. At the same time, the relationship may operate in the opposite direction. Heart failure can adversely affect oral health through impaired tissue perfusion, nutritional deterioration, frailty, cognitive impairment, polypharmacy, and reduced capacity for self-care, which may facilitate periodontal deterioration and functional oral decline.[12,19–22]

Several uncertainties remain. Heart failure-specific studies are limited by observational designs, heterogeneous definitions of oral disease, inconsistent periodontal assessment, and incomplete adjustment for confounding factors.[8,9,12,16,17,23] Prospective studies combining standardized oral phenotyping with detailed HF characterization, coronary microvascular assessment, and biomarker profiling are scarce. Convincing evidence that periodontal treatment improves clinically relevant HF outcomes is also lacking.

In this state-of-the-art review, we examine the proposed oral–HF axis by integrating evidence from periodontology, cardiovascular biology, immunology, and HF research. We focus on inflammation, oxidative stress, endothelial dysfunction, and coronary microvascular dysfunction (CMD) as candidate mechanisms connecting oral disorders with HF. We pay particular attention to the distinction

between HF-specific observations and mechanisms extrapolated from the broader cardiovascular literature, as well as to methodological limitations that should guide future mechanistic and interventional studies.

Objectives

To critically evaluate the emerging oral–HF axis by integrating epidemiological, mechanistic, experimental, and interventional evidence, with particular emphasis on bidirectionality, biological plausibility, causal inference, and potential clinical implications.

Materials and methods

Search strategy and evidence classification

This state-of-the-art review was based on a targeted literature search focused primarily on publications from 2022 to 2026. The search was last updated on September 8, 2026. An initial core set of relevant studies was expanded through searches of MEDLINE via PubMed and the reference lists of key publications. The core search combined terms related to HF: heart failure (HF), heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), with oral and periodontal concepts (periodontitis, periodontal disease, oral health, oral microbiome, tooth loss). Additional targeted searches incorporated mechanistic terms including inflammation, oxidative stress, mitochondrial dysfunction, endothelial dysfunction, CMD, fibrosis, remodeling, frailty, and periodontal treatment. We included earlier landmark or mechanistically important studies when necessary. Studies were identified and selected iteratively as individual themes of the review were developed; predefined systematic screening criteria were not applied.

The selection of publications was guided by thematic relevance, study design, and their contributions to the epidemiology, mechanistic plausibility, bidirectionality, causal interpretation, or interventional implications of the oral–HF axis. Human studies directly examining oral or periodontal disease in relation to HF were prioritized. Broader cardiovascular evidence was used only to inform intermediate biological mechanisms when direct HF-specific evidence was limited, without equating these data with proof of an oral contribution to HF. Observational human, experimental, genetic, and interventional evidence were considered separately. The narrative synthesis considered exposure definitions, consistency, potential residual confounding and reverse causation, and relevance to HF. This targeted search was neither systematic nor exhaustive; no formal study-level risk-of-bias assessment or de novo quantitative synthesis was performed.

Results

Heart failure as a systemic multiorgan syndrome

Heart failure is increasingly understood as a systemic, multiorgan syndrome rather than an isolated disorder of cardiac pump function. Hemodynamic abnormalities, congestion, and neurohormonal activation interact with inflammation, oxidative stress, endothelial dysfunction, and metabolic disturbances, allowing cardiac and extracardiac abnormalities to reinforce one another.[14,24] Aging adds another layer through cellular senescence, mitochondrial dysfunction, impaired tissue repair, and vascular stiffening.[14] Sleep fragmentation may further contribute through autonomic, hemodynamic, and metabolic stress.[25]

Inflammatory activation is a frequent component of HF, although it is not uniform across phenotypes or patients. Interleukin-6 (IL-6) was more consistently associated with cardiovascular mortality in HFpEF than in HFrEF, in line with a stronger contribution of comorbidity-related inflammatory activation in HFpEF.[24,26] Simple blood-derived indices also reflect this systemic component. Neutrophil-to-lymphocyte and lymphocyte-to-C-reactive protein (CRP) indices have been associated with congestion, nutritional status, physical performance, and mortality, while other complete blood count-derived indices have been proposed as accessible measures of systemic immune activity.[27–30] These markers remain nonspecific and should not be interpreted as evidence of a particular inflammatory source.

The comorbidity-driven model of HFpEF provides a framework for how systemic inflammation may affect myocardial function. In the Paulus–Tschöpe paradigm, obesity, diabetes, renal dysfunction, and other comorbidities promote systemic inflammation, coronary microvascular endothelial activation, oxidative stress, reduced nitric oxide (NO) bioavailability, and impaired NO–cyclic guanosine monophosphate (cGMP)–protein kinase G (PKG) signaling.[13] These abnormalities may increase cardiomyocyte stiffness and contribute to remodeling. The model is biologically coherent but remains an integrative rather than fully demonstrated causal pathway. Coronary microvascular dysfunction is common in HFpEF and is associated with diastolic abnormalities and adverse outcomes, although prevalence and effect estimates depend on the diagnostic method.[15]

The cardiorenal axis is a key example of organ interdependence in HF. Renal dysfunction occurs across the ejection-fraction spectrum and is associated with worse symptoms, impaired health status, and poorer prognosis.[14,31] Venous congestion and neurohormonal activation may further impair renal function. In HFpEF, albuminuria, tubular-injury markers, urinary oxidative-stress products, and proteomic signatures suggest systemic vascular, inflammatory, and fibrotic involvement beyond reduced glomerular filtration[3]. Thus, ejection fraction

and conventional cardiac biomarkers capture only part of the biological burden of HF.[3,14]

Metabolic organs and adipose tissue also contribute to HF pathophysiology. Epicardial adiposity may promote local inflammatory signaling, ventricular interaction, and pericardial constraint, whereas body mass index (BMI) does not adequately capture risk related to fat distribution.[32,33] In non-diabetic patients with acute HF, a higher triglyceride–glucose index was associated with in-hospital mortality.[18] Experimental metabolomic studies further link altered substrate utilization and impaired mitochondrial ATP production with adverse ventricular remodeling, although their relevance to human HF remains uncertain.[34]

Skeletal-muscle deterioration, malnutrition, and frailty are important components of the systemic HF phenotype. Sarcopenia, impaired muscle quality, and reduced strength are associated with poorer physical performance and prognosis.[35,36] Malnutrition and inadequate protein intake frequently coexist with inflammation and are linked to mortality, readmission, and functional dependence, although these associations vary with the method of nutritional assessment and may partly reflect reverse causation.[21,37] Frailty extends beyond physical impairment to nutritional, cognitive, and psychosocial deficits and is associated with greater hospitalization burden and reduced quality of life.[19,38,39]

The brain is also involved in this multiorgan network. Cerebral hypoperfusion, vascular injury, and inflammatory processes may contribute to cognitive dysfunction, while prospective observations indicate changes in depressive symptoms, cognitive function, and self-care behavior in patients with HF.[22,40] These abnormalities are clinically relevant because they affect patients' ability to follow treatment recommendations, maintain adequate nutrition, and perform daily self-care.[22,40,41] Oral hygiene and access to dental care may be affected for the same reasons.

Heart failure can therefore be viewed as a disorder in which cardiovascular dysfunction interacts with renal, metabolic, muscular, nutritional, inflammatory, and neurocognitive abnormalities. This systemic background is important when considering oral disease. Chronic periodontal inflammation may add to an already increased inflammatory and oxidative burden, whereas HF-related frailty, malnutrition, cognitive impairment, and reduced self-care may simultaneously worsen oral health. The oral–HF axis should therefore be examined within this wider multiorgan network rather than as an isolated interaction between periodontal tissues and the myocardium.[12,14,24]

Oral inflammatory and functional disorders

Oral abnormalities relevant to HF include distinct inflammatory, structural, and functional phenotypes that should not be combined under a single concept of poor oral health. Active gingival inflammation, established periodontitis, tooth loss, and impaired oral function represent different disease features or consequences and require standardized clinical assessment.[9,23,42,43] This distinction is particularly relevant when oral findings are interpreted as possible markers of systemic inflammatory exposure.

Periodontal inflammatory activity can be characterized beyond the diagnosis of periodontitis itself. Bleeding on probing (BOP) and periodontal inflamed surface area (PISA) reflect the extent of clinically active inflammatory tissue, whereas attachment loss and radiographic bone loss mainly describe cumulative structural damage.[23] Biological studies also indicate an inflammatory and redox component of active oral disease. Salivary IL-18 decreased, and IL-35 increased after non-surgical periodontal therapy.[44] Stage III periodontitis was associated with higher serum CRP and mannose-binding lectin and lower SIRT-1, although short-term treatment did not significantly change CRP or SIRT-1.[45] Acute odontogenic infection was accompanied by higher salivary IL-6, macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor alpha (TNF-α) and altered antioxidant enzyme activity,[46] while changes in oxidative and nitrosative markers were reported during treatment of gingivitis in obese young adults.[47] These observations support active local and systemic inflammatory or redox alterations in oral disease, but they do not establish cardiac involvement.

Heart failure-specific observations are more limited. Left ventricular assist device (LVAD) recipients had more missing teeth and more severe periodontitis than controls, together with limited use of interdental hygiene measures.[48] In a subsequent cohort including patients with severe HF, LVAD support, or previous heart transplantation, nearly 90% of dentate participants had stage III–IV periodontitis. Higher BOP was associated with cardiac/driveline and extracardiac bacterial infections, whereas higher PISA was associated with extracardiac infection and sepsis. Neither oral variable, however, independently predicted cardiac/driveline infection or survival after multivariable analysis.[17] Periodontal inflammation may therefore identify patients with advanced HF and greater clinical vulnerability, but the available data do not demonstrate an independent causal role. Broader cardiovascular evidence supports mechanistic plausibility, while periodontal intervention studies have mainly demonstrated changes in surrogate rather than clinical cardiovascular outcomes.[49,50]

Oral functional deterioration represents a different, less-investigated component of this relationship. Periodontitis is associated with poorer oral-health-related quality of life and functional limitation, and advanced disease can be accompanied by tooth loss and impaired mastication.[9,51] Edentulism and absence of functional dentition remain common in older populations.[10] Xerostomia, plaque accumulation, and impaired oral care are also frequent during critical illness.[42,52] Such abnormalities could contribute to nutritional vulnerability, although studies of oral

nutritional supplementation in HF have focused on anorexia and malnutrition rather than dental or masticatory causes of reduced intake.[53] Prospective HF studies combining standardized assessment of periodontal inflammatory burden with oral function, nutritional status and frailty are still missing.

Epidemiological evidence for the oral–heart failure association

Heart failure-specific epidemiological evidence remains less extensive than that available for atherosclerotic CVD. Most studies are observational and have assessed periodontitis, tooth loss, edentulism, dental attendance, or oral-hygiene behaviors, while studies testing whether oral interventions influence HF outcomes are virtually absent.[54]

In the Atherosclerosis Risk in Communities (ARIC) cohort, periodontal disease was associated with incident HFrEF, whereas the association with HFpEF was weaker and statistically inconclusive. Edentulism showed stronger associations with both HF phenotypes, with approximately twofold higher risks after adjustment for cardiovascular risk factors and biomarkers.[55] These findings suggest that cumulative oral-health deterioration may be more strongly associated with HF than periodontitis considered as a single exposure.

Large South Korean cohorts provide further observational evidence. In a cohort of 161,286 adults without HF at baseline, toothbrushing at least 3 times a day was associated with modestly lower HF incidence in a fully adjusted model (hazard ratio (HR) = 0.88, 95% confidence interval (95% CI): 0.83–0.94), whereas professional dental cleaning was not statistically significant after adjustment for all oral-health variables (HR = 0.94, 95% CI: 0.89–1.01). At least 22 missing teeth were associated with greater HF incidence (HR = 1.31, 95% CI: 1.11–1.55).[16] Among adults with type 2 diabetes, extensive tooth loss was associated with incident HF, with modest associations reported for oral-hygiene behaviors.[56] A separate nationwide cohort of 4,440,970 adults reported a graded association of tooth loss with incident HF (adjusted HR = 1.016, 95% CI: 1.013–1.019, per additional missing tooth).[57] These behavioral and structural oral-health indicators are nonspecific and do not demonstrate periodontal causality.

The interpretation of this association is less straightforward. Tooth loss is not specific to periodontitis and may result from periodontal disease, dental caries, or both. It also accumulates with aging and is associated with smoking, diabetes, socioeconomic disadvantage, access to dental care, and long-term health behaviors.[10] Edentulism and extensive tooth loss may therefore reflect cumulative oral and systemic vulnerability rather than ongoing periodontal inflammatory activity.

Data from patients with established HF are fewer. In stable HFrEF, moderate or severe periodontitis was common, and greater periodontal severity was associated with higher N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations in a subgroup of younger patients.[58] Among older adults hospitalized with acute HF, oral-health problems coexisted with malnutrition, cognitive impairment, and reduced physical function. Poorer oral status also predicted deterioration in activities of daily living during hospitalization.[59] These observations indicate that oral abnormalities are frequent in clinically vulnerable HF populations, but they do not establish whether oral disease contributes to HF severity or mainly accompanies advanced systemic disease.

Residual confounding remains difficult to exclude. Several determinants of poor oral health also increase HF risk, and this problem is particularly relevant when oral exposures are based on self-report, dental claims, or administrative records rather than standardized clinical examination. Reverse causation is equally plausible, because frailty, malnutrition, cognitive impairment, and functional dependence may reduce oral hygiene, dental attendance, and access to treatment in patients with HF.[20,60]

Comparison between studies is further complicated by differences in periodontal assessment. Periodontitis has been defined using full-mouth examination, partial recording protocols, probing depth, clinical attachment loss, self-report, or insurance diagnoses.[61] These approaches do not measure the same phenotype and may partly explain differences in reported associations.

Current epidemiological evidence therefore supports an association between adverse oral-health indicators and HF, with the most reproducible findings concerning tooth loss and edentulism. Evidence for periodontitis as an independent HF risk factor is less consistent. Associations observed for oral-hygiene behaviors are also difficult to separate from socioeconomic status, healthcare use, and other health-related behaviors. At present, epidemiological data do not establish causality. Table 1[16,54–59] summarizes the main HF-specific epidemiological evidence linking periodontal and oral health with HF, along with its key limitations and implications for the oral–HF axis.

Biological pathways linking oral disease with heart failure

Oral dysbiosis, microbial translocation, and functional alterations of the oral microbiome

A mechanistic interpretation of the oral–HF association starts at the periodontal biofilm, where dysbiosis reflects community-level interactions rather than the action of a single pathogen.[62,63] This ecological perspective is increasingly incorporated into cardiovascular models of the oral microbiome.[64,65] Antimicrobial adjuncts support a microbial contribution to periodontal disease but

Table 1. Heart failure-specific epidemiological evidence linking periodontal and oral health with heart failure

Study	Population and design	Oral exposure	HF endpoint	Main finding	Key limitations	Interpretation for the oral-HF axis
Chang et al.[16]	Nationwide South Korean population cohort; >160,000 adults without HF at baseline	Missing teeth, toothbrushing frequency, professional dental cleaning	Incident HF	Fully adjusted HF associations: toothbrushing ≥3 times/day: HR = 0.88 (95% CI: 0.83–0.94); professional dental cleaning: HR = 0.94 (95% CI: 0.89–1.01), not statistically significant; ≥22 missing teeth: HR = 1.31 (95% CI: 1.11–1.55).	Administrative exposure measures; healthy user bias; socioeconomic and healthcare-use confounding.	Suggests an oral-health signal, but behavioral associations are not evidence of periodontal causality.
Chen et al.[54]	Meta-analysis plus Mendelian randomization	Periodontitis	HF overall, HFrEF, and HFpEF	Observational synthesis supported a positive association, whereas Mendelian randomization did not identify a significant causal effect of acute or chronic periodontitis on HF.	Genetic instrument validity depends on periodontal phenotype definition; observational studies remain heterogeneous.	Key discordance between conventional epidemiology and genetic causal inference.
Molinsky et al.[55]	ARIC prospective cohort	Clinically assessed periodontal status and edentulism	Incident HFrEF and HFpEF	Clinically assessed periodontal disease was associated with incident HFrEF (HR = 1.69, 95% CI: 1.18–2.43), but its association with HFpEF was inconclusive (HR = 1.35, 95% CI: 0.98–1.86); edentulism was associated with both phenotypes.	Observational design; residual confounding; edentulism is a cumulative and nonspecific oral endpoint.	Supports an association, but does not isolate active periodontal inflammation as the causal exposure.
Huh et al.[56]	Nationwide cohort of adults with type 2 diabetes	Dental disease, tooth loss, oral-hygiene behaviors	Incident HF	Extensive tooth loss was associated with higher HF risk, while regular toothbrushing and professional cleaning showed small inverse associations.	Diabetes-specific population; claims-based exposure assessment; healthy user bias.	Supports association in a high-risk population, but exposure specificity is limited.
Lee et al.[57]	Large nationwide population cohort	Number of missing teeth	Incident HF and other cardiovascular outcomes	Each additional missing tooth was associated with higher HF hazard: adjusted HR = 1.016 (95% CI: 1.013–1.019).	Tooth loss does not identify active periodontitis and reflects cumulative oral, behavioral, and systemic factors.	Strong marker of cumulative vulnerability rather than direct evidence of an inflammatory oral-HF pathway.
Sharma et al.[58]	Cross-sectional study in stable chronic HFrEF	Clinical periodontitis severity	HF status and NT-proBNP	Moderate or severe periodontitis was common; greater periodontal severity was associated with higher NT-proBNP in a younger subgroup.	Cross-sectional design; subgroup finding; no temporal inference.	Shows coexistence of periodontal disease and HF severity markers, not directionality.
Uemura et al.[59]	Older adults hospitalized with acute HF	Oral-health status	Physical function and in-hospital functional decline	Poorer oral status coexisted with malnutrition, cognitive impairment, and reduced physical function and predicted deterioration in activities of daily living.	Oral exposure not specific to periodontitis; outcome was functional decline rather than HF incidence or progression.	Supports oral health as a marker of vulnerability in HF populations.

Representative HF-specific observational and synthesis evidence evaluating associations of periodontal disease, tooth loss, oral-hygiene behaviors, and oral-health status with prevalent or incident HF. Differences in periodontal exposure definition, HF ascertainment, population characteristics, and adjustment strategy limit direct comparison and causal interpretation. ARIC – atherosclerosis risk in communities; HR – hazard ratio; 95% CI – 95% confidence interval; EF – ejection fraction; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; HFrEF – heart failure with reduced ejection fraction; NT-proBNP – N-terminal pro-B-type natriuretic peptide; OR – odds ratio.

do not identify a systemic route,[66] while treatment-related cytokine and serum biomarker changes do not demonstrate microbial translocation.[44,45]

Interpretation of microbiome studies requires caution because microbial profiles depend on sampling and analytical methods; moreover, different oral niches are not interchangeable measures of exposure, and taxonomic composition does not necessarily reflect microbial activity.[65]

Direct characterization of the oral microbiome in HF has only recently begun. In a case–control study of 63 patients with HF and 31 controls, HF status and New York Heart Association (NYHA) class were associated with differences

in supragingival bacterial and fungal community structure.[67] Rather than a generalized loss of microbial diversity, HF was characterized by specific bacterial and fungal signatures and altered bacterial–fungal co-abundance relationships, some of which were associated with more advanced NYHA class.[67] Functional differences were inferred rather than directly measured, and the cross-sectional design precluded determination of directionality.

A further HF-specific study found differences in oral microbial profiles associated with emotional disorders and systemic inflammatory indices.[68] Together, these small cross-sectional studies indicate variation of the oral ecosystem across HF populations but do not establish a general HF-specific microbial signature or directionality.[67,68]

Systemic exposure becomes more plausible when periodontal barrier integrity is compromised. Pocket formation increases epithelial permeability, while PISA estimates the extent of inflamed pocket epithelium exposed to the subgingival biofilm.[69,70] *Porphyromonas gingivalis* lipopolysaccharide (LPS) and gingipain are biologically relevant bacterial components,[71,72] but experimental reconstruction of these components does not demonstrate their passage through the human periodontal barrier. Transient bacteremia after periodontal procedures or tooth brushing provides direct human evidence that the periodontal barrier can be crossed.[73,74] Procedure-related bacteremia is considered in dental recommendations for patients with vascular prostheses, but does not imply persistent bloodstream infection.[75] Detection of periodontal bacterial DNA in blood provides additional evidence of systemic exposure, but bacterial DNA does not indicate viable bacterial dissemination.[76] Human studies have also associated periodontitis and periodontal inflammatory burden with circulating LPS/endotoxemia, although systemic endotoxin is not specific to an oral source.[77–79] Overall, bacteremia and circulating microbial products remain plausible oral–cardiovascular routes, but evidence is substantially stronger for CVD in general than for HF specifically.[8,64,65]

Altered oral microbial function may provide a complementary mechanism that does not require dissemination. The enterosalivary nitrate–nitrite–NO pathway partly depends on oral nitrate-reducing bacteria and may contribute to vascular homeostasis.[80] Dysbiosis may therefore involve not only acquiring pro-inflammatory properties but also losing beneficial microbial functions. In 9 older patients with HFrEF and nine age-matched controls, oral nitrate-reducing capacity and salivary nitrite concentrations were lower in HFrEF.[81] Across the combined cohort, nitrate-reducing capacity correlated with measures of aerobic capacity, although these associations were not significant when groups were analyzed separately.[81] The study did not sequence the microbiome, demonstrate differences in circulating nitrite, or assess endothelial or coronary microvascular function. It therefore supports impaired oral nitrate-reducing function in HFrEF, but not a proven pathway to systemic NO deficiency or vascular dysfunction.

For HF, these observations do not yet form a demonstrated causal chain. Severe periodontitis was associated cross-sectionally with HF with reduced or mildly reduced ejection fraction, but not with HFpEF or HF overall.[82] Gut-microbiome studies show that microbe-derived signals can reach the circulation and participate in HF-related immune pathways,[83,84] but cannot establish an oral source, while human evidence remains mixed on whether inflammation is a causal driver of HF rather than a marker or response to disease.[85] Recent HF-specific studies suggest altered oral bacterial and fungal community structure and preliminary evidence of impaired nitrate-reducing function.[67,68,81] A useful working model may therefore distinguish a potential pathogenic gain of function, involving barrier disruption and intermittent microbial exposure, from a potential homeostatic loss of function, involving impairment of physiological activities such as nitrate reduction. Whether these processes modify HF, result from HF, or operate bidirectionally remains unresolved; their most immediate mechanistic implication is possible convergence on systemic immune-inflammatory pathways.

Systemic inflammation and immune activation

One potential consequence of periodontal barrier disruption is amplification of systemic immune-inflammatory activity. Cumulative periodontal inflammatory burden, quantified by periodontal inflamed surface area, has been associated with circulating CRP.[86] Similarly, in a multicentre study of systemically healthy individuals, periodontal treatment reduced serum IL-6 and high-sensitivity CRP (hsCRP), with changes in periodontal inflamed surface area particularly related to changes in IL-6.[87] These findings link the extent of active periodontal inflammation with systemic inflammatory activity, although reductions in nonspecific biomarkers after treatment do not establish periodontitis as an independent causal source of systemic inflammation.

A more direct oral–cardiac route may coexist with this systemic pathway. Experimental evidence indicates that translocation of *P. gingivalis* to atrial tissue can be accompanied by increased IL-6, galectin-3, and transforming growth factor (TGF)-β1 signaling and greater fibrosis, while human observations have associated atrial *P. gingivalis* burden with atrial fibrosis.[88] However, these findings come from an odontogenic infection model and patients with atrial fibrillation (AF) rather than HF, so they support biological plausibility without demonstrating an oral microbial contribution to HF remodeling.

Periodontal-derived inflammatory or microbial stimuli could also converge on innate immune pathways already implicated in HF.[7,24,89] Pattern-recognition signaling can activate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and the NLRP3 (NLR family pyrin domain containing 3) inflammasome, promoting caspase-1-dependent maturation of IL-1β and IL-18 and downstream

IL-6-mediated acute-phase responses.[24,90] Experimental studies support a functional role of this pathway in cardiac injury: in a mouse model of structural cardiomyopathy, genetic deletion of Nlrp3 reduced caspase-1 activation and circulating IL-1β and improved systolic function, while IL-1 receptor blockade attenuated myocardial inflammation and dysfunction.[91] These findings demonstrate that inflammasome-dependent signaling can contribute to cardiac dysfunction, but they do not identify periodontal inflammation as the initiating stimulus.

In HFpEF, inflammation may arise from aging, obesity, diabetes, and renal dysfunction,[14,92,93] while circulating mediators and immune-cell abnormalities cannot identify its source.[26,85,94] Interventional evidence confirms the biological relevance of inflammatory signaling.[95] In CANTOS, IL-1β inhibition with canakinumab was associated with a dose-dependent trend toward fewer HF hospitalizations among patients with previous myocardial infarction (MI) and residual inflammatory risk.[96] However, the HF analysis was exploratory; the population was not selected for established HF, and the findings provide no evidence that the inflammatory activity being modified originated from periodontal disease.

A more appropriate interpretation may therefore be an additive inflammatory-burden model. Periodontal inflammation need not initiate HF to be biologically relevant; persistent exposure to inflammatory mediators, microbial components, or intermittent bacteremia could hypothetically add to inflammation generated by HF-related comorbidities. Such convergence may be particularly plausible in HFpEF, where multiple extracardiac stressors are thought to promote systemic inflammation and vascular dysfunction.

Collectively, the available evidence supports a biologically coherent framework in which active periodontal inflammation may contribute to systemic immune-inflammatory activity, while microbial dissemination provides an additional potential route of oral–cardiac communication.[86–88] Separately, experimental and clinical data show that innate immune pathways, particularly NLRP3–IL-1 signaling, can contribute to myocardial dysfunction and HF-related outcomes.[85,91,96] The critical missing link is prospective evidence connecting quantified periodontal inflammation or microbial exposure with systemic immune activation and subsequent HF development or progression. The inflammatory component of the oral–HF axis should therefore be regarded as mechanistically plausible, but not as an established causal pathway.

Oxidative stress and mitochondrial dysfunction

Oxidative stress is increasingly recognized as a component of periodontal tissue injury, reflecting excessive reactive oxygen species (ROS) generation relative to antioxidant and repair capacity. In periodontitis, neutrophil activation, inflammatory signaling, and NADPH oxidases contribute to ROS production, while antioxidant systems including SOD1, GPX1, and thioredoxin-related pathways may be impaired.[97–100] This redox imbalance is detectable beyond periodontal tissues. Patients with periodontitis show higher circulating oxidative stress indices and lower antioxidant capacity, and periodontal inflamed surface area is independently associated with systemic oxidative stress.[101] Serum and salivary malondialdehyde (MDA) and 8-oxo-2'-deoxyguanosine (8-OHdG) may decrease after periodontal therapy, although changes in antioxidant enzymes are inconsistent across populations and disease grades.[102,103] Meta-analytic data therefore support a systemic oxidative signature of periodontitis but also substantial biomarker heterogeneity and limited source specificity.[98,104]

Mitochondria may amplify periodontal redox injury. Experimental and human periodontal data indicate mitochondrial Ca^{2+} overload, increased signaling involving voltage-dependent anion channel 1 (VDAC1) and the mitochondrial calcium uniporter (MCU), mitochondrial DNA (mtDNA) leakage, impaired oxidative phosphorylation, defective PTEN-induced kinase 1 (PINK1)-dependent mitophagy, and increased mitochondrial reactive oxygen species (mtROS).[105–108] *Porphyromonas gingivalis* can also promote dynamin-related protein 1 (Drp1)-dependent mitochondrial fission, loss of membrane potential, and adenosine triphosphate (ATP) depletion in vascular cells, providing a plausible cardiovascular bridge without demonstrating myocardial injury.[109]

Cardiac effects remain predominantly preclinical. Experimental periodontitis has been associated with cardiac lipid peroxidation, increased 8-OHdG, oxidative stress, and mitochondrial DNA damage,[110,111] while antioxidant interventions attenuated cardiac redox abnormalities.[11,112] Complementary experiments using *P. gingivalis* LPS demonstrated cardiac oxidative stress associated with toll-like receptor 4 (TLR4)–NADPH oxidase 4 (NOX4) signaling and increased xanthine oxidase expression, accompanied by cardiomyocyte apoptosis, myocardial fibrosis, and systolic dysfunction. These changes were attenuated by pharmacological inhibition of TLR4 or treatment with allopurinol.[113,114] These models support biological plausibility but do not reproduce chronic human periodontitis.

More disease-proximal evidence comes from experimental HFpEF, where *P. gingivalis*-associated periodontitis aggravated diastolic dysfunction and myocardial injury, although mitochondrial function was not directly assessed.[115] Mitochondrial dysfunction is, however, well established in HF. Human advanced HF myocardium shows impaired oxidative capacity associated with inflammation,[116] while experimental HFrEF and HFpEF models demonstrate impaired respiration, ATP production, increased mtROS, and defective mitophagy.[34,117] Human HFpEF proteomics further supports disruption of mitochondrial organization and oxidative phosphorylation.[118] Altered redox regulation and immunometabolic signaling provide additional mechanistic context.[119–123]

Collectively, periodontitis is associated with local and systemic redox imbalance and increasingly with mitochondrial dysfunction, while experimental oral inflammatory exposures can induce cardiac oxidative injury. Nevertheless, direct human evidence that periodontitis causes myocardial mitochondrial dysfunction and thereby accelerates HF remains lacking.

Endothelial and microvascular dysfunction

Endothelial dysfunction may represent a vascular interface between periodontal inflammation and HF. Periodontitis is associated with impaired peripheral endothelial function, and periodontal therapy may improve flow-mediated dilation (FMD) despite heterogeneity.[124–127] However, FMD reflects conduit-artery responsiveness rather than coronary microvascular function, and periodontal intervention studies have not assessed coronary flow reserve, myocardial blood flow, invasive microvascular resistance, or HF outcomes.[124–127]

Experimental data provide a mechanistic bridge. *Porphyromonas gingivalis* can impair endothelial redox and NO signaling and promote endothelial activation and mitochondrial dysfunction.[109,128,129] These findings support biological plausibility but remain predominantly preclinical.

This mechanism may be relevant to HFpEF, where comorbidity-driven systemic inflammation has been proposed to induce coronary microvascular endothelial activation, oxidative stress, reduced NO bioavailability, and impaired NO–cGMP–PKG signaling, thereby increasing cardiomyocyte stiffness and remodeling.[13] Human myocardial studies support key elements of this paradigm, demonstrating increased endothelial E-selectin and intercellular adhesion molecule 1 (ICAM-1) expression, NADPH oxidase 2 (NOX2)-related oxidative stress, endothelial nitric oxide synthase (eNOS) uncoupling, and reduced myocardial cGMP–PKG activity.[130] Systemic endothelial dysfunction has also been associated with subsequent HF development,[131] while impaired endogenous NO production occurs in HFrEF as well,[132] indicating that endothelial injury is not specific to HFpEF. Contemporary data further show immuno-hemostatic abnormalities in HFpEF, but circulating endothelial markers are not uniformly elevated.[133]

Coronary microvascular dysfunction is nevertheless common in HFpEF. PROMIS-HFpEF reported impaired coronary flow reserve in 75% of patients and linked it with systemic endothelial dysfunction, albuminuria, NT-proBNP, and HF severity.[134] Positron emission tomography (PET) studies associated impaired coronary flow reserve with worse diastolic function and future HFpEF hospitalization,[135] and follow-up data linked CMD with HF-related events.[136] A meta-analysis estimated CMD in approx. 58% of HFpEF patients and associated it with more severe diastolic dysfunction and higher risk of death or HF hospitalization.[15] Importantly, CMD includes both endothelium-dependent and endothelium-independent abnormalities.[137] Human tissue studies also demonstrate coronary microvascular rarefaction associated with myocardial fibrosis.[138]

Direct oral–HFpEF evidence remains preclinical. In mice, *P. gingivalis*-associated periodontitis reduced NO bioavailability, worsened diastolic dysfunction, decreased coronary microvascular density, and increased inflammation and fibrosis.[115] Human studies of peripheral endothelial function in periodontitis and studies of CMD in HFpEF arise from distinct populations and assess different vascular outcomes. Brachial flow-mediated dilation does not directly measure coronary microvascular function. No human study identified in this review establishes that clinically quantified periodontal inflammatory burden causes CMD in HFpEF or that periodontal therapy improves coronary microvascular function or HF outcomes.[115,124–127]

Cardiac fibrosis and remodeling

The inflammatory, oxidative, mitochondrial, and microvascular abnormalities discussed above may ultimately converge on structural cardiac remodeling. This process includes cardiomyocyte hypertrophy, cardiac fibroblast activation, altered extracellular matrix (ECM) turnover, and interstitial fibrosis, which increase myocardial stiffness and may impair ventricular function.[139] Systemic inflammation, immune-cell activation, aging, inflammasome signaling, and mitochondrial dysfunction can contribute to these changes,[14,24,85,116,140–142] while fibroadipogenic progenitor cells may represent an additional cellular component of profibrotic remodeling in failing human myocardium.[143] In HFpEF, inflammation, endothelial dysfunction, congestion, and fibrosis frequently coexist and may reduce ventricular compliance and functional reserve.[3,144] AMPK-, PI3K–AKT-, and Nrf2-related pathways further link hypertrophic, metabolic, and redox responses, although their clinical relevance to HFpEF remains uncertain.[120,145,146]

Periodontitis could add to this profibrotic environment by increasing systemic inflammatory and oxidative burden. Periodontal studies have demonstrated alterations in CRP, SIRT-1, antioxidant defense, and paraoxonase-1 activity, with smoking modifying some treatment-related biomarker responses.[45,97,147] Human cardiac data remain limited. In patients with controlled hypertension, greater periodontal inflammatory burden, as quantified by PISA, was associated with mild alterations in global longitudinal strain, although the clinical significance remains uncertain.[148] In Multi-Ethnic Study of Atherosclerosis (MESA), self-reported periodontal disease was associated with a small increase in myocardial extracellular volume fraction in men, but not in women, and was not associated with myocardial scar.[149] A large population-based study subsequently found small differences in left ventricular (LV) volumes, mass, and function across periodontal measures and disease stages.[150] These associations remain susceptible to residual confounding and reverse causality.

Experimental evidence is more consistent. Persistent periodontitis intensified post-MI fibrosis in mice through expansion of collagen-producing SiglecF$^+$ neutrophils and activation of cardiac fibroblasts.[151] In a murine HFpEF model, periodontitis increased myocardial inflammation, interstitial and pericapillary fibrosis, coronary microvascular rarefaction, and diastolic dysfunction.[115] Together, these findings support a disease-modifying model in which periodontal inflammation may amplify remodeling when the myocardium is already exposed to pathological stress, rather than initiating fibrosis independently.

Cardiac remodeling can partially regress during contemporary HF treatment, and sustained reverse remodeling occurs in a subset of patients with HFrEF.[139,152,153] Serial CMR with T1 mapping and extracellular volume assessment provides a noninvasive approach to quantify diffuse myocardial fibrosis over time.[154] Periodontitis should therefore be regarded as a potential additional contributor to the inflammatory-fibrotic burden, not as a proven cause of myocardial fibrosis. Future studies should combine standardized periodontal phenotyping with CMR, myocardial strain imaging, circulating fibrosis markers, and repeated HF characterization.

Phenotype-specific and bidirectional nature of the oral–HF axis

The oral–HF axis is unlikely to be uniform across HF phenotypes or disease stages. HFpEF is characterized by aging, multimorbidity, systemic inflammation, and CMD, providing a plausible setting in which periodontal inflammation could act as an additional extracardiac stressor.[13,15,26,155] Human data, however, do not consistently support greater periodontal susceptibility in HFpEF. Periodontitis was more clearly associated with HFrEF than HFpEF in ARIC, while severe periodontitis was associated with prevalent HFrEF/HFmrEF but not HFpEF in another population study; periodontal severity has also been linked to NT-proBNP in stable HFrEF.[55,58,82] Experimental periodontitis worsens HFpEF through inflammatory, microvascular, and fibrotic pathways, whereas reduced oral nitrate-reducing capacity in HFrEF suggests that HF phenotype may also influence oral microbial function.[81,115]

The relationship may also operate in the opposite direction. Advanced HF and LVAD populations frequently show substantial periodontal disease and impaired oral-health behavior.[17,48] More recently, HF was associated with greater oral-health burden in UK Biobank, while pressure-overload HF induced gingival inflammation and impaired periodontal remodeling in mice.[12] Broader dental cohorts suggest that systemic disease burden may accompany poorer periodontal status, although findings are inconsistent.[156,157] Xerostomia may represent another reverse pathway: in 371 patients with chronic HF, 64.8% reported xerostomia, with fluid restriction, thirst, edema, and treated diabetes associated with greater symptom intensity.[158] Diabetes-related xerostomia is independently associated with poorer oral-health-related quality of life.[159] Cognitive impairment and declining self-care may further compromise oral maintenance.[22,40,160]

Frailty and nutritional deterioration may amplify this bidirectional interaction. Sarcopenia, malnutrition, reduced protein intake, and functional dependence are common in HF and are associated with prognosis.[19–21,39] Contemporary data further support nutritional impairment and substantial hospitalization burden in HF populations.[161,162] In older adults, tooth loss, unmet prosthetic needs, and oral symptoms may accompany functional vulnerability and reduce oral-health-related quality of life.[163,164] Nevertheless, these studies do not establish that oral functional deterioration independently accelerates HF progression. Heart failure-specific longitudinal studies that combine standardized periodontal assessment with oral function, nutrition, frailty, and clinical outcomes are still needed.

Overall, the oral–HF axis is better viewed as a dynamic, phenotype- and stage-dependent bidirectional interaction. Oral inflammation may increase systemic stress, whereas established HF may progressively worsen periodontal and oral function. Prospective studies with repeated oral and cardiac phenotyping are required to determine the temporal sequence and relative contribution of both directions.

Periodontal treatment and clinical implications in heart failure

The potential systemic relevance of periodontal therapy should be distinguished from its established local efficacy. Non-surgical treatment consistently reduces probing depth and bleeding on probing, including in patients with systemic comorbidities.[165] Adjunctive approaches such as melatonin or local drug delivery may further improve selected periodontal endpoints, but their effects remain treatment-specific.[166,167] Changes in inflammatory biomarkers after non-surgical therapy also confirm that periodontal inflammation is biologically modifiable.[44,45] Local treatment success, however, does not itself demonstrate cardiovascular or HF benefit.

The strongest systemic intervention signal concerns CRP and IL-6. Meta-analyses of randomized trials support reductions in CRP and, less consistently, IL-6 after periodontal treatment,[168,169] while multicenter data relate reduced periodontal inflammatory burden to changes in IL-6 and hsCRP.[87] Responses are heterogeneous and time-dependent, varying with sampling interval and patient phenotype.[170] A recent meta-analysis found the apparent CRP effect more convincing in uncontrolled pre–post comparisons than in limited controlled evidence,[171] while a randomized type 2 diabetes mellitus (T2DM) study showed numerical but nonsignificant between-group reductions in hsCRP and IL-6 despite substantial periodontal improvement.[172] Treatment protocols may also influence biomarker trajectories.[173] Thus, periodontal therapy can

modify selected systemic inflammatory markers, but these changes should not be equated with reduced HF risk.

Redox effects remain uncertain: periodontal therapy can modify selected oxidative-stress markers,[45,47,174–176] but antioxidant responses are inconsistent,[177] and no study demonstrates reduced myocardial oxidative stress in HF.

Vascular outcomes remain surrogate. Periodontal therapy may improve FMD and arterial stiffness,[124–127] but findings are inconsistent,[178] and clinical cardiovascular benefit remains unproven.[179] Flow-mediated dilation should not be interpreted as evidence of improved coronary microvascular function or HF prognosis.

Heart failure-related biomarkers and cardiac functional measures remain sparse. In patients without established HF, periodontal treatment reduced NT-proBNP,[180] while a randomized study in T2DM showed a modest improvement in E/e' without changes in LV mass index; reductions in NT-proBNP, hsCRP, and IL-6 were not significant between groups.[172] These findings indicate biomarker or functional modulation rather than HF treatment. Direct HF evidence is limited to a small uncontrolled pilot in patients with congestive HF and periodontitis, in which NT-proBNP and TNF-α changed after treatment[181]; concomitant HF therapy precluded causal attribution. Cross-sectional associations between periodontitis and NT-proBNP provide context only.[58] Current data therefore do not demonstrate modification of the HF phenotype.

Evidence remains insufficient to establish whether periodontal therapy modifies clinical HF outcomes. Periodontal treatment has not demonstrated reductions in major cardiovascular events or mortality in interventional or observational studies,[182,183] while favorable findings for AF recurrence remain non-randomized and disease-specific.[184] No completed trial has shown that periodontal therapy reduces HF hospitalization or mortality.[185,186] Importantly, this absence of demonstrated benefit should not be interpreted as evidence that periodontal treatment has no effect on these outcomes. Rather, adequately powered HF-specific trials with sufficient follow-up and clinical endpoints have not yet been completed.

This lack of HF-modifying evidence does not make oral care clinically irrelevant. Heart failure-specific observations associate oral-hygiene-related characteristics with HF status,[187] while dental cohorts demonstrate a high prevalence of systemic comorbidity and support structured medical-history assessment.[156,188] Clinical examination remains necessary even when self-reported periodontal symptoms are informative,[157] and advanced HF or critical illness may further complicate oral care.[48,52] Treatment should remain proportionate: systemic antibiotics did not improve uncomplicated early healing after regenerative periodontal surgery,[189,190] local adjuncts mainly affect periodontal endpoints,[167] and oral surgery may itself provoke a transient systemic inflammatory response.[191,192] The high healthcare burden of HF supports coordinated management of relevant extracardiac disease,[162] while systemic and nutritional determinants of periodontal status caution against attributing biomarker changes solely to dental intervention.[193] Contemporary cardiovascular guidance also does not recognize periodontal treatment as a proven strategy to reduce cardiovascular events.[186] A dedicated randomized trial, Periodontitis Treatment and Heart Failure (NCT07036289), is currently evaluating whether periodontal therapy can influence NT-proBNP in patients with HFrEF/HFmrEF.[194] Although this study will not establish effects on hospitalization or mortality, it represents an important step toward testing the oral–HF hypothesis in a disease-specific interventional setting. Periodontal therapy in HF should therefore be regarded as appropriate treatment of oral inflammatory disease, while its role as an HF-modifying intervention remains investigational.

Table 2[87,127,168,169,172,178,180,181–184,194] summarizes selected periodontal intervention studies and their relevance to HF.

Discussion

From association to causation: Current evidence, limitations, and future directions

The epidemiological association between periodontal disease and HF is increasingly reproducible, but reproducibility does not establish causality. Prospective studies report associations with incident or prevalent HF.[54,55,82] Leelaviwat et al. reported a pooled odds ratio (OR) of 1.58 (95% CI: 1.15–2.18) across 3 cohort studies including 17,807 participants, with substantial heterogeneity (I^2 = 78.4%).[195] A subsequent meta-analysis of 7 cohorts comprising more than 370,000 participants reported a similar crude pooled association, risk ratio (RR) of 1.58 (95% CI: 1.20–2.07), but with very high heterogeneity (I^2 = 93.8%).[196] Adjusted estimates were not pooled because individual studies differed substantially in covariate selection and model specification.[196] Pooled OR and crude RR should not be treated as interchangeable, and neither estimate alone establishes an independent causal effect. The included studies also varied in periodontal and HF definitions and in whether HF was incident or prevalent. These findings support a reproducible epidemiological signal, but its magnitude is sensitive to study design, periodontal definition, population characteristics, and analytical approach.

A major problem is the inconsistent definition of periodontal exposure. Studies use full-mouth examination, partial recording, administrative diagnoses, self-reported symptoms, tooth loss, edentulism, toothbrushing, or dental attendance, although these measures are not biologically equivalent. Self-reported measures have limited sensitivity for clinically defined periodontitis,[197] questionnaire performance varies across populations,[198] and partial-mouth protocols can alter prevalence and risk associations.[199] Contemporary staging and grading also show incomplete agreement,[200] supporting the need for standardized phenotyping.[201] Tooth loss may

Table 2. Periodontal intervention studies and their relevance to heart failure

Study	Population, n	Intervention and follow-up	Outcome	Main quantitative finding	HF relevance	Key limitation
Matsuda et al.[87]	Systemically healthy patients with periodontal disease; n = 153 overall; responder analysis n = 145 (72 low, 73 high responders)	Initial periodontal treatment; variable treatment period; median 175.5 days in low responders and 203 days in high responders	Systemic inflammation	On log-transformed analysis, IL-6 decreased (β = −0.12, 95% CI: −0.19 to −0.05; p < 0.001) and hsCRP decreased (β = −0.18, 95% CI: −0.27 to −0.08; p < 0.001). The treatment-response interaction was significant for IL-6 (β = −0.07, 95% CI: −0.14 to −0.002; p = 0.044) but not for hsCRP.	Supports biological modifiability of systemic inflammatory activity after periodontal treatment.	No HF or cardiovascular population; no randomized untreated comparator; nonspecific surrogate biomarkers.
Tonetti et al.[127]	Severe generalized periodontitis; n = 120 randomized: 61 intensive treatment, 59 community care	Intensive periodontal therapy vs community periodontal care; assessments to 180 days	Peripheral endothelial function	FMD was transiently worse at 24 h, then greater after intensive treatment at 60 days (+0.9%, 95% CI: 0.1–1.7; p = 0.02) and 180 days (+2.0%, 95% CI: 1.2–2.8; p < 0.001).	Demonstrates modulation of a peripheral vascular surrogate after periodontal intervention.	Brachial FMD is not coronary microvascular function; non-HF population; no HF outcomes.
Luthra et al.[168]	Systematic review / meta-analysis of 26 RCTs; n = 2579	Periodontal treatment vs control; studies with ≥6-month follow-up	CRP	At 6 months, CRP was lower after treatment: MD = −0.69 mg/L (95% CI: −0.97 to −0.40; p < 0.001; I^2 = 66%) across 19 studies. No treatment effect was demonstrated in 4 studies with ≥12-month follow-up.	Strong evidence that periodontal therapy can modify a systemic inflammatory surrogate relevant to HF biology.	Not HF-specific; substantial heterogeneity; biomarker rather than cardiac or HF clinical outcome.
Meng et al.[169]	Meta-analysis of 21 RCTs; aggregate participant number NR as a single total in the source	NSPT vs no treatment, OHI or control periodontal treatment; follow-up varied across trials	CVD-related inflammatory and vascular risk markers	CRP: WMD = −0.63 mg/L (95% CI: −1.02 to −0.24; p < 0.01; I^2 = 66%); IL-6: WMD = −0.73 pg/mL (95% CI: −0.89 to −0.57; p < 0.01; I^2 = 30%). FMD was not significantly improved: WMD = +1.70% (95% CI: −1.63 to 5.03; p = 0.32).	Supports effects on selected systemic inflammatory markers but does not establish improvement in vascular function or HF outcomes.	Heterogeneous populations and follow-up; surrogate outcomes; not HF-specific.
Wang et al.[172]	T2DM with stage III/IV-equivalent periodontitis and no major cardiovascular complications; n = 58 randomized (29/29); echocardiographic analysis 28 control / 27 treatment	NSPT vs OHI with delayed periodontal therapy; 6 months	LV diastolic function, LVMI and biomarkers	Adjusted between-group treatment effect on mean E/e' was -1.66 (95% CI: −2.64 to −0.68; p < 0.01). LVMI was unchanged. NT-proBNP, hsCRP, and IL-6 decreased numerically but without significant between-group effects.	Provides randomized evidence for modulation of an HF-relevant cardiac functional surrogate.	Not an HF trial; preserved LVEF, no major CVD complications; small sample, 6-month follow-up and surrogate echocardiographic endpoint.
Molina et al.[178]	Stage III/IV periodontitis with established CVD; 36 randomized, 35 assessed at baseline	Nonsurgical periodontal intervention vs control periodontal care; 6 months	Endothelial function	At 6 months, FMD was 10.14% in control vs 9.72% in test group; between-group difference 0.42 percentage points (95% CI: −3.63 to 4.46; p = 0.831).	Shows that favorable peripheral vascular effects are not uniformly reproducible in higher-risk CVD populations.	Small, underpowered pilot; attrition; surrogate vascular outcome; not HF-specific.
Isola et al.[180]	Stage III periodontitis without established HF; n = 48, 24 FM-SRP vs 24 SOC	Full-mouth scaling and root planing vs minimal standard oral care; 1, 3, and 6 months	NT-proBNP and inflammatory/ CVD-related biomarkers	At 6 months, NT-proBNP was 102 vs 127 pg/mL in FM-SRP vs SOC (p = 0.004).	Demonstrates modulation of an HF-relevant biomarker after periodontal treatment.	Participants did not have HF; biomarker reduction does not establish improvement in HF phenotype or clinical outcomes.
Czerniuk et al.[181]	Patients with congestive HF and periodontitis; n = 39 overall, with small marker-specific test/ reference subsets	Periodontal treatment with scaling / root planing; reassessment after 3–9 months (mean: approx. 6 months); concomitant HF treatment continued	NT-proBNP and TNF-α	In the principal test subgroup, NT-proBNP decreased by approx. 29.7% from baseline after periodontal treatment; biomarker changes were reported without a conventional randomized treatment-control architecture.	Directly HF-specific pilot evidence showing biomarker change following periodontal treatment.	Small, nonrandomized pilot; unconventional reference groups; concurrent HF therapy; biomarker rather than clinical endpoint; causal attribution not possible.

Table 2. Periodontal intervention studies and their relevance to heart failure – cont.

Study	Population, n	Intervention and follow-up	Outcome	Main quantitative finding	HF relevance	Key limitation
Sen et al.[182]	Stroke/TIA with moderate-to-severe periodontitis; n = 280, 140 intensive vs 140 standard	Intensive vs standard periodontal treatment; 12 months	Death, MI or recurrent stroke	Primary composite occurred in 11/140 (8%) vs 17/140 (12%); HR = 0.65 (95% CI: 0.30–1.38). Intensive treatment was not superior.	Provides randomized clinical-outcome context for cardiovascular prevention.	Population and outcome were not HF-specific; CI was wide and included no effect.
Michalowicz et al.[183]	Periodontitis with CAD, CBVD and/or T2DM; 9503 unique patients	Periodontal treatment/ maintenance vs untreated; mean clinical follow-up 7.5 years CAD, 4.8 years CBVD, and 5.3 years T2DM	Hospitalization, CV outcomes and mortality	Treatment plus maintenance was associated with lower all-cause hospitalization: CAD: OR = 0.71 (95% CI: 0.55–0.92); CBVD: OR = 0.73 (95% CI: 0.56–0.94); T2DM: OR = 0.80 (95% CI: 0.64–0.99). Adjusted cardiovascular events and mortality were not significantly reduced.	Provides long-term healthcare-utilization context but not evidence of HF modification.	Retrospective observational design; nonrandom treatment selection and residual/ healthy-user confounding; not HF-specific.
Miyauchi et al.[184]	Patients undergoing initial AF ablation; n = 288; 97 accepted periodontal treatment	Periodontal treatment during the blanking period; mean follow-up 507 ±256 days	AF recurrence	Periodontal treatment was associated with lower AF recurrence: adjusted HR = 0.393 (95% CI: 0.215–0.719; p = 0.002).	Provides disease-specific evidence that periodontal intervention may have cardiac relevance outside HF.	Prospective but nonrandomized; AF rather than HF; residual selection and confounding cannot be excluded.
NCT07036289[194]	Periodontitis with HF of intermediate/ reduced EF plus non-HF periodontal comparator; actual total enrollment n = 80	Three-arm randomized trial; SRP + OHI vs HF periodontal control with delayed treatment; primary comparison through 6 months	Primary: change in blood NT-proBNP	No results available. Registry status: Active, not recruiting. Primary endpoint is change in NT-proBNP from baseline to 6 months.	Most directly HF-specific randomized interventional test of the oral-HF hypothesis to date.	No efficacy results posted; actual arm-specific analyzed sample sizes unavailable; biomarker primary endpoint, not hospitalization or mortality.

Selected periodontal intervention studies relevant to systemic inflammation, vascular function, cardiac biomarkers, cardiac functional surrogates, and clinical cardiovascular outcomes. Evidence is most consistent for improvement in periodontal status and selected systemic inflammatory markers. Effects on peripheral endothelial function are heterogeneous, while direct evidence for modification of the HF phenotype remains sparse. No completed randomized HF-specific trial included in this review has established reductions in HF hospitalization or mortality. This reflects the current absence of adequately powered HF-specific outcome trials rather than demonstrated absence of benefit. For systematic reviews and meta-analyses, aggregate sample sizes are reported only when explicitly provided by the source publication and were not reconstructed from individual trial reports. AF – atrial fibrillation; CAD – coronary artery disease; CBVD – cerebrovascular disease; 95% CI – 95% confidence interval; CRP – C-reactive protein; CVD – cardiovascular disease; FMD – flow-mediated dilation; FM-SRP – full-mouth scaling and root planing; HF – heart failure; HFmrEF – heart failure with mildly reduced ejection fraction; HFrEF – heart failure with reduced ejection fraction; HR – hazard ratio; hsCRP – high-sensitivity C-reactive protein; IL – interleukin; LV – left ventricular; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index; MD – mean difference; MI – myocardial infarction; NR – not reported; NSPT – non-surgical periodontal therapy; NT-proBNP – N-terminal pro-B-type natriuretic peptide; OHI – oral-hygiene instructions; OR – odds ratio; PISA – periodontal inflamed surface area; RCT – randomized controlled trial; SOC – standard oral care; SRP – scaling and root planing; T2DM – type 2 diabetes mellitus; TIA – transient ischemic attack; TNF-α – tumor necrosis factor alpha; WMD – weighted mean difference.

show stronger associations with HF than clinically defined periodontitis,[55] but also reflects aging, caries, smoking, diabetes, socioeconomic factors, and dental history; thus, stronger associations with edentulism do not imply greater effects of active periodontal inflammation.

Confounding further limits interpretation. Periodontitis and HF share aging, smoking, diabetes, obesity, renal dysfunction, socioeconomic deprivation, multimorbidity, and limited healthcare access.[8,14,202] Periodontal disease predicted later CVD and vice versa despite extensive adjustment,[203] while PAROKRANK showed a modest adjusted association with cardiovascular events.[204] Residual confounding may persist because adherence, nutrition, lifetime smoking exposure, and healthcare-seeking behavior are measured imperfectly,[203] with healthy-user effects particularly relevant to preventive dental behaviors.[205] Causal diagrams may help distinguish confounders, mediators, and colliders,[206] while negative controls may detect residual behavioral bias.[207]

Directionality is also uncertain. Heart failure may worsen oral health through frailty, medication burden, impaired self-care, nutritional decline, and reduced access to dental treatment. Longitudinal evidence supports reverse directionality, with CVD predicting later periodontal disease,[203] and HF associated with gingival inflammation and impaired periodontal remodeling.[12] Observed

associations may therefore reflect an oral contribution to HF, a consequence of HF, shared vulnerability, or combinations of these processes.

Mendelian randomization (MR) offers a complementary approach to causal inference but depends on valid genetic instruments and an accurate representation of the exposure. Chen et al. reported no statistically significant MR association between genetically proxied acute or chronic periodontitis and HF.[54] The exposure datasets included 367 acute and 3,046 chronic periodontitis cases, with 10 and 16 genetic instruments, respectively, selected using a relaxed association threshold ($p < 5 \times 10^{-6}$); reported F-statistics exceeded 10. Inverse-variance weighting (IVW) was supplemented by MR-Egger, weighted median, mode-based, heterogeneity, pleiotropy, and leave-one-out analyses. However, nonsignificant sensitivity tests do not establish that all instrumental-variable assumptions hold.[54] Similar null findings have been reported for coronary atherosclerosis,[208] and a recent systematic review found limited evidence for direct causal effects across systemic outcomes.[209] These results weaken a simple model in which periodontitis independently causes HF, but do not exclude clinically relevant effects. Genetically proxied periodontal diagnoses do not match clinically quantified inflammatory burden, such as bleeding on probing or periodontal inflamed surface area. Limited case numbers, exposure misclassification, possible horizontal pleiotropy, ancestry restrictions, and limited power to detect modest effects constrain interpretation. The null MR findings weaken a simple independent causal account but do not exclude context-dependent modification of HF in patients with active periodontal inflammation. Better genetically instrumented periodontal phenotypes and triangulation with prospective and interventional studies are needed.[210–214]

Periodontal genome-wide association studies (GWAS) often rely on self-reported painful gums, bleeding gums, or loose teeth rather than standardized inflammatory phenotypes,[210] so instrument strength does not ensure biological fidelity. Pleiotropy, ancestry, sample overlap, and phenotype definition remain important,[211,212] and shared genetic loci may coexist with a null direct MR estimate.[213] Hypertension provides a useful comparator, where MR and periodontal intervention have been combined within a stronger triangulation framework[214]; comparable evidence is not yet available for HF.

Mechanistic plausibility should be distinguished from causal completion. Periodontitis is associated with systemic inflammation; periodontal treatment can modify selected inflammatory markers,[86,87] and inflammatory pathways contribute to HF biology.[85,96] These observations are compatible but do not demonstrate mediation. Periodontal oxidative imbalance and oxidative injury in HF do not establish an oral origin of myocardial oxidative stress; likewise, peripheral endothelial dysfunction in periodontitis and CMD in HFpEF do not establish a periodontal cause of CMD. Formal mediation requires temporality and appropriate causal analysis,[215] while biological plausibility should not convert parallel observations into causality.[216]

Experimental HFpEF and cardiac remodeling models provide the strongest mechanistic signal, although their translational relevance to human HF remains limited. Periodontitis and *P. gingivalis* LPS can induce cardiac functional, inflammatory, oxidative, and fibrotic changes,[217–219] but these models do not reproduce chronic polymicrobial human disease. In experimental HFpEF, periodontitis worsened an established cardiometabolic phenotype rather than initiating HF,[115] supporting disease modification over disease initiation.

Human evidence is weakest at the myocardial and coronary microvascular steps. Small observational signals exist for strain, extracellular volume, and ventricular geometry,[148–150] while large imaging datasets show statistically detectable but quantitatively small CMR differences associated with periodontal disease.[220] No direct human study identified in this review has linked clinically quantified periodontal inflammatory burden with myocardial blood flow, myocardial flow reserve, invasive coronary flow reserve, or index of microvascular resistance. These are central measures of CMD,[221] and peripheral FMD cannot fill this gap.

Table 3[15,54,55,62–65,67–70,74,76–79,81,82,86–88,97,98,101–104,109–115,124–129,134–138,148–151,195,196,217–219] presents the triangulation of evidence across the proposed oral–HF pathway.

Current evidence supports 3 overlapping interpretations: a direct causal model, a disease-modifier model, and a shared-vulnerability model. The latter 2 are better supported than a simple independent causal pathway. Future studies should combine repeated full-mouth periodontal assessment with adjudicated HF outcomes and detailed cardiac phenotyping. Direct CMD assessment should use PET or invasive coronary physiology, while serial CMR, strain, multiomics, and formal mediation analyses could test remodeling and pathway transmission. Better genetic instruments based on clinically defined periodontitis are needed. Observational treatment studies may benefit from target trial emulation.[222,223] Given the prognostic relevance of nutritional status in HF, future oral–HF studies should also include standardized assessment of malnutrition and dietary intake.[224] Ultimately, HF-specific randomized trials must evaluate functional status, quality of life, hospitalization, and mortality, not biomarkers alone.

Limitations of the study

This review integrates observational, experimental, genetic, and intervention evidence while distinguishing biological plausibility from causality, HF phenotypes, and bidirectionality. The literature search was targeted, iterative, and relevance-based, rather than systematic or exhaustive; relevant studies may therefore have been omitted and selection bias cannot be excluded. No formal study-level risk-of-bias assessment or de novo meta-analysis was

Table 3. Triangulation of evidence across the proposed oral–HF pathway

Proposed pathway step	Human oral or periodontal evidence	Human HF evidence (direct oral–HF studies or HF pathophysiology)	Experimental or genetic evidence	Current inference	Critical missing evidence
Oral dysbiosis to periodontal inflammation	Human microbiome and clinical studies support dysbiosis, increased community biomass, and active periodontal inflammation.[62–65]	Small HF studies show altered oral bacterial and fungal community structure and preliminary functional differences.[67,68,81]	Mechanistic models support polymicrobial synergy and dysbiosis, but do not establish HF directionality.	Relatively well supported locally; HF directionality uncertain.	Longitudinal HF cohorts with standardized periodontal phenotyping, repeated microbiome sampling and functional assays.
Periodontal barrier disruption to microbial exposure	Pocket epithelial disruption, procedure-related bacteremia and endotoxemia support intermittent systemic exposure.[69,70,73,74,76–79]	No direct demonstration of oral microbial delivery to human failing myocardium or HF-specific vascular tissue.	Experimental evidence supports extraoral dissemination of *P. gingivalis*, including to atrial tissue.[88]	Biologically plausible, but source attribution remains incomplete.	Source-specific demonstration of oral microbial products reaching HF-relevant tissues in humans.
Periodontitis to systemic inflammation	PISA is associated with circulating CRP; periodontal treatment can reduce selected inflammatory markers, including IL-6 and hsCRP.[86,87]	HF-specific studies do not show that periodontal inflammation is the dominant or initiating source of the inflammatory HF phenotype.	Inflammatory pathways including NLRP3-IL-1 signaling contribute to cardiac dysfunction in experimental models.[91]	Moderate evidence for systemic inflammatory effects; causal mediation to HF unproven.	Prospective mediation linking quantified periodontal burden to systemic inflammation and subsequent HF outcomes.
Periodontitis to systemic oxidative stress	Human studies and meta-analyses support systemic redox imbalance and associations with periodontal inflammatory burden.[97,98,101–104]	No direct evidence that periodontal disease is a source of myocardial oxidative stress in human HF.	Animal periodontitis and *P. gingivalis* LPS models show cardiac oxidative injury and mitochondrial damage.[110–115]	Moderate mechanistic plausibility.	Human source attribution and longitudinal assessment linking periodontal exposure to myocardial redox or mitochondrial dysfunction.
Periodontitis to peripheral endothelial dysfunction	Periodontitis is associated with impaired brachial FMD; treatment can improve FMD in some studies.[124–127]	Peripheral endothelial measures are relevant to HF risk but are not equivalent to coronary microvascular physiology.	Endothelial cell models support impaired NO signaling, oxidative stress, inflammatory activation, and mitochondrial dysfunction.[109,128,129]	Moderate evidence for peripheral vascular effects.	Direct demonstration that periodontal inflammatory burden alters coronary endothelial or microvascular function.
Periodontitis to CMD	No direct human periodontal study identified using myocardial blood flow, myocardial flow reserve, invasive coronary flow reserve, or microvascular resistance.	CMD is common and prognostically relevant in HFpEF,[15,134–138] but its oral source has not been demonstrated.	Periodontitis worsened coronary microvascular rarefaction and reduced NO bioavailability in experimental HFpEF.[115]	Not adequately demonstrated in humans.	Prospective periodontal phenotyping paired with PET myocardial perfusion, stress CMR, or invasive coronary physiology.
Periodontitis to myocardial fibrosis and remodeling	Small human studies report associations with strain, myocardial extracellular volume, and LV geometry.[148–150]	No prospective HF study demonstrates periodontal-induced remodeling or fibrosis progression.	Animal studies show greater fibrosis and remodeling after periodontal inflammatory exposure, especially in pre-existing cardiac stress.[115,151]	Preliminary human evidence; stronger experimental support.	Serial CMR T1 mapping, extracellular volume, and strain with repeated periodontal assessment and confounder control.
Periodontitis to incident or progressive HF	HF-specific cohorts and meta-analyses show a reproducible but heterogeneous association.[54,55,82,195,196]	Human evidence for HF progression is sparse; direct mediation through CMD or remodeling has not been shown.	HF-specific MR found no statistically significant association for genetically proxied periodontal disease,[54] while experimental models suggest potential disease modification.[115,217–219]	Association reproducible; causal effect unresolved.	Triangulated prospective studies with clinically defined periodontitis, adjudicated HF outcomes, repeated mediators, and improved genetic instruments.
Periodontal treatment to HF modification	Periodontal therapy improves local disease and can modify selected systemic inflammatory, redox, and vascular surrogate markers.[87,124–127,168,169,174–177,180]	Direct HF intervention evidence is limited to small or ongoing studies; no completed trial has shown reduced HF hospitalization or mortality.[181,185,194]	No experimental or genetic evidence can substitute for clinical outcome trials.	HF-modifying benefit unproven.	HF-specific randomized trials assessing symptoms, functional status, hospitalization and mortality in addition to biomarkers.

Evidence is separated across human periodontal studies, HF-specific human observations and experimental or genetic studies to distinguish biological plausibility from demonstrated causal mediation. The qualitative terms in the "Current inference" column are interpretive summaries for this review and do not represent a formal GRADE assessment. The table highlights the discontinuity between relatively well-supported proximal periodontal and systemic processes and the limited direct human evidence linking oral inflammatory burden to CMD, myocardial remodeling, and clinically manifest HF. Human HF evidence includes both studies directly measuring oral or periodontal exposures and studies of HF pathophysiology without oral assessment; these should not be regarded as equivalent evidence for an oral contribution to HF. CMD – coronary microvascular dysfunction; CMR – cardiac magnetic resonance; CRP – C-reactive protein; FMD – flow-mediated dilation; HF – heart failure; HFpEF – heart failure with preserved ejection fraction; hsCRP – high-sensitivity C-reactive protein; LV – left ventricular; NO – nitric oxide; PET – positron emission tomography; PISA – periodontal inflamed surface area.

undertaken. The small number of studies in the available HF-specific meta-analyses limits reliable evaluation of publication bias, and statistical heterogeneity should not be confused with biological heterogeneity. Several pathways rely on preclinical data or extrapolation from broader cardiovascular research rather than directly paired periodontal and HF measurements in humans.

Conclusions

Current observational evidence supports associations between adverse oral-health indicators and HF, whereas associations specifically involving clinically defined periodontitis remain heterogeneous. Systemic inflammation, oxidative stress, altered NO signaling, endothelial dysfunction, and myocardial remodeling are plausible intermediate mechanisms, but their connection to periodontal exposures in human HF remains largely indirect. Interpretation is constrained by shared risk factors, non-equivalent oral exposure definitions, confounding, reverse causation, and the absence of supportive MR evidence for a simple direct causal effect.

The oral–HF axis should therefore be viewed as a working biological framework rather than an established causal pathway. Periodontitis may act as a context-dependent disease modifier, while HF itself may adversely affect oral health. Periodontal assessment and treatment remain appropriate as part of comprehensive care, but periodontal therapy cannot currently be considered HF-modifying treatment. Future studies should combine standardized periodontal phenotyping with detailed HF characterization, direct coronary microvascular assessment, serial cardiac imaging, and clinically meaningful outcomes. The oral–HF axis is a compelling research framework, but its causal significance remains unproven.

Use of AI and AI-assisted technologies

Not applicable.

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