Review

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# Mechanistic Insights Into the Periodontal-Atherosclerotic Axis: From Oral Inflammation to Cardiovascular Pathology

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**This descriptive review synthesizes mechanistic and clinical evidence on the periodontal disease (PD)–atherosclerotic cardiovascular disease (ASCVD) axis to clarify how oral inflammation, bacterial translocation, immune dysregulation, and oxidative stress may influence vascular pathology and to identify where causal inference and interventional evidence remain insufficient. We searched PubMed, Web of Science, ScienceDirect, and Google Scholar for studies on microbial translocation, systemic inflammation, endothelial dysfunction, and interventional outcomes. Evidence supports a robust epidemiological association between PD and ASCVD; proposed mechanisms prominently involve *Porphyromonas gingivalis*-driven immune modulation and endothelial injury. Periodontal therapy consistently reduces inflammatory biomarkers and improves surrogate vascular measures, while effects on hard cardiovascular outcomes are suggestive but not definitive. Recognizing PD as a modifiable oral inflammatory condition may refine cardiovascular risk assessment and motivate integrated prevention, while future work should prioritize well-designed randomized trials with standardized PD/ASCVD phenotyping.**

**Keywords:** periodontal disease; inflammation; atherosclerosis; coronary artery disease

## Introduction

Periodontal disease (PD) is a common chronic inflammatory condition affecting the soft and hard tissues surrounding the teeth, with a high global prevalence, especially in adults over the age of 35. The disease is characterized by inflammation, gum recession, and loss of attachment to the teeth, which can lead to tooth mobility and, ultimately, tooth loss. On the other hand, atherosclerotic cardiovascular disease (ASCVD) is a condition characterized by plaque development and progression in the arteries, which can lead to severe cardiovascular events such as heart attacks, strokes, and peripheral artery disease. For decades, ASCVD has been recognized as a leading cause of morbidity and mortality worldwide [1,2]. More recently, numerous studies have suggested a link between PD and increased cardiovascular risk, sparking significant interest in the potential role of oral health in overall cardiovascular risk management [3–5]. This article aims to explore the association between PD and ASCVD, investigate potential mechanisms underlying this link, and review clinical studies that support or challenge this connection.

PD may contribute to the development, progression, and instability of atherosclerotic plaques in the arteries [6,7]. Two main hypotheses have been proposed to explain this relationship: (1) periodontal pathogens directly enter the bloodstream, and (2) the disease increases systemic inflammation, leading to higher levels of pro-inflammatory mediators [8–12]. Interestingly, some studies suggest that managing one of these conditions may have a beneficial effect on the other, potentially improving both periodontal and cardiovascular health simultaneously [13,14].

Given the increasing recognition of the association between PD and ASCVD, early detection and treatment of PD could play a crucial role in preventing cardiovascular events [13]. Addressing PD may help reduce the overall burden of ASCVD and improve long-term health outcomes [14]. However, to establish a definitive causal link between these two diseases, further experimental studies, both *in vitro* and *in vivo*, with longer follow-up periods, are needed.

A key limitation in this literature is confounding (e.g., smoking, diabetes, socioeconomic status, and healthcare access), which may inflate or obscure the PD and ASCVD association in observational designs. Accordingly, the cen-

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tral uncertainty is not the existence of an epidemiological association, which is well supported, but the extent to which it is causal and independent of shared risk factors. This review, therefore, separates what is established (association, plausible mechanisms, biomarker changes) from what remains unresolved (causality, effect size after rigorous adjustment, and impact on hard outcomes).

## Methodology

This is a descriptive literature review with a structured search strategy. The aim is to integrate mechanistic and clinical evidence on the PD and ASCVD axis and to highlight unresolved questions without attempting exhaustive retrieval or quantitative synthesis. We searched PubMed, Web of Science, ScienceDirect, and Google Scholar through January 2025, combining keywords ("periodontal disease", "atherosclerosis", "cardiovascular disease", "oral microbiome", "systemic inflammation", "bacterial translocation", "periodontal therapy", "cardiovascular outcomes") with Boolean operators. Titles/abstracts were screened, followed by full-text review. Eligibility emphasized studies elucidating microbial translocation, systemic inflammation and oxidative stress, endothelial dysfunction, and interventional signals. Earlier seminal sources were included to preserve mechanistic continuity. No risk of bias assessment or meta-analysis was performed.

## Mechanisms Underlying ASCVDs and the Contribution of PD

The pathogenesis of atherosclerosis involves a complex interplay of endothelial dysfunction, lipid accumulation, inflammatory responses, and oxidative stress [15–17]. The endothelium regulates vascular tone and maintains blood fluidity [18]. Factors such as hypertension, hyperlipidemia, and smoking can impair endothelial function, increasing permeability to lipoproteins and promoting leukocyte adhesion. This dysfunction is a critical initial step in atherogenesis [19]. Low-density lipoprotein (LDL) particles infiltrate the subendothelial space, where they undergo oxidation. Oxidized LDL (ox-LDL) is cytotoxic and elicits an inflammatory response, attracting monocytes that differentiate into macrophages. These macrophages engulf ox-LDL, transforming into foam cells and contributing to fatty streak formation [20]. Chronic inflammation plays a central role in the progression of atherosclerosis. Activated macrophages and other immune cells release a spectrum of cytokines, including pro-inflammatory mediators such as interleukin-1 beta (IL-1$\beta$), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-17 (IL-17), and interferon-gamma (IFN-$\gamma$), as well as anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-$\beta$). Additionally, chemokines such as monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1 (MIP-1/CCL3, CCL4), RANTES (CCL5), and CXCL8 (IL-8) contribute to the recruitment of leukocytes and the perpetuation of local inflammation. This pro-inflammatory microenvironment exacerbates endothelial dysfunction, promotes plaque development, and accelerates disease progression [17,21,22]. An imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to oxidative stress, which exacerbates endothelial dysfunction and inflammation. ROS can oxidize lipids and proteins within the arterial wall, further promoting atherogenesis [23–25].

The proposed mechanisms linking PD to atherosclerosis include systemic inflammation, bacterial dissemination, molecular mimicry, and oxidative stress. PD elevates systemic inflammatory markers, such as C-reactive protein (CRP) and IL-6, which are also associated with ASCVD. This systemic inflammation may contribute to endothelial dysfunction and plaque instability [8]. Pathogens from periodontal pockets can enter the bloodstream, leading to transient bacteremia. Bacteria such as *Porphyromonas gingivalis* (*P. gingivalis*) have been detected within atherosclerotic plaques, suggesting direct microbial involvement in plaque formation and progression [6]. Structural similarities between periodontal pathogens and host tissues may induce autoimmune responses, where the immune system attacks endothelial cells, promoting atherogenesis [26]. PD can increase oxidative stress levels, contributing to lipid oxidation and endothelial damage, thereby facilitating atherosclerotic changes [23]. Recent studies have highlighted the importance of maintaining oral hygiene in reducing cardiovascular risk [5,14,27]. For instance, flossing once a week has been associated with a significant reduction in stroke risk, underscoring the potential systemic benefits of oral care [27].

### *PD and Systemic Inflammation*

PD is primarily an inflammatory condition that affects the tissues supporting the teeth, caused by the accumulation of bacteria in the oral cavity and an imbalance between the host and the oral bacterial communities. The immune response to these bacteria results in inflammation in the gums and surrounding tissues. Bacterial lipopolysaccharides (LPS) from these periodontal bacteria stimulate monocytes to release inflammatory mediators such as TNF-$\alpha$, prostaglandins, interleukins, and proteolytic enzymes like matrix metalloproteinases [28,29]. This inflammatory response is not limited to the periodontal area, where increased levels of local inflammatory cytokines and other mediators can be found in gingival crevicular fluid, saliva, and gingival tissues [30].

Over time, this chronic inflammation may have systemic effects, leading to the release of pro-inflammatory cytokines and other immune mediators into the bloodstream, as individuals with periodontitis show higher serum levels of inflammatory markers than healthy controls [31]. This

systemic inflammation is thought to play a role in the development of atherosclerosis by promoting the formation of plaque within blood vessels, which is a key characteristic of ASCVD. Elevated systemic inflammatory markers have been linked to an increased risk of cardiovascular diseases (CVDs), establishing a potential connection between PD and heart health [32,33].

Several interleukins, including interleukin-1 (IL-1), interleukin-4 (IL-4), IL-6, IL-8, and interleukin-18 (IL-18), have been investigated for their possible shared role in the development of periodontitis and other systemic inflammatory conditions [34,35]. Increased levels of IL-6 in the serum have been observed in individuals with moderate chronic periodontitis compared to those with healthy or less severe conditions, even after adjusting for known risk factors [36]. A case-control study by Widén *et al.* (2016) [37] revealed a strong association between PD and CVD with an odds ratio of 7.5 for patients with acute coronary syndrome also presenting periodontitis. While inflammatory markers like IL-8 and vascular endothelial growth factor were found to be significantly elevated in the acute coronary syndrome group compared to controls, these levels did not correlate with the participants' periodontal health. This suggests that, although periodontitis was almost five times more common in those with CVD, the link between serum cytokine levels and acute coronary syndrome was independent of periodontal status.

Periodontitis is a chronic inflammatory condition primarily caused by bacterial microorganisms, leading to severe inflammation that results in the destruction of the tooth-supporting structures and can ultimately lead to tooth loss. If left untreated, it leads to irreversible periodontal defects and further tooth loss. In addition to its local effects, periodontitis is linked with various systemic diseases, including CVDs, gastrointestinal diseases, diabetes and insulin resistance, Alzheimer's disease, respiratory tract infection, and adverse pregnancy outcomes [38].

Research has shown a strong link between oral dysbiosis and CVD, as well as how CVD can influence the composition of the oral microbiota [39]. In the case of PDs, the presence of increased Gram-negative bacteria, including *P. gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, may worsen CVD by initiating local inflammation. This local response, in turn, triggers systemic inflammation, immune activation, oxidative stress, and platelet aggregation—factors closely associated with CVD. Specific pathogens, like *S. mutans* and *P. gingivalis*, are notably higher in patients who suffer from both PD and atherosclerosis [39,40].

Emerging evidence also suggests a bidirectional relationship between the oral microbiota and CVD, where systemic inflammation and immune activation caused by CVD can affect the oral microbiota [41]. Bacteria from the oral cavity can invade the bloodstream, a process that is potentially facilitated by oral gut microbiota transfer and bacteremia. This invasion may intensify systemic inflammation, setting off a chain reaction that further disrupts the delicate balance of the oral microbial environment [42].

Moreover, metabolites produced by the oral microbiota are gaining attention for their potential role in cardiometabolic health. For instance, bacterial surface molecules such as LPS and bacterial flagellins can stimulate the production of pro-inflammatory mediators and cytokines. These molecules activate inflammatory pathways like nuclear factor kappa-B (NF-$\kappa$B) and matrix metalloproteinase 9 (MMP-9), further contributing to inflammation and immune responses [43]. In the case of *Aggregatibacter actinomycetemcomitans*, a pathogen associated with chronic periodontitis, it releases leukotoxin A, which destroys white blood cells by disrupting cellular structures. This leads to hypercitrullination and the release of altered proteins, potentially triggering autoimmune responses that might contribute to the development of atherosclerosis [41,44]. In addition to these well-known bacteria, other species such as *Prevotella intermedia, Prevotella nigrescens*, *Campylobacter rectus*, *Parvimonas micra*, *Eubacterium timidum*, *Eubacterium brachy*, and *Eubacterium saphenum* have also been linked to both oral dysbiosis and the onset of CVD [41].

Another key aspect of the immune response in the development of atherosclerosis involves heat shock proteins (HSPs), a family of proteins that help protect cells under stress. Both human cells and bacteria like *P. gingivalis* produce HSPs. In the case of *P. gingivalis*, its equivalent of HSP60, called GroEL, can trigger both humoral and cellular immune responses in humans [45]. This immune response may result in chronic activation because antibodies designed to target bacterial HSPs can mistakenly cross-react with human HSP60 due to structural similarities. This sustained immune activation promotes inflammation within the walls of arteries, leading to plaque accumulation composed of cholesterol, immune cells, and cellular debris [46]. Over time, this plaque narrows the arteries, restricting blood flow and increasing the risk of cardiovascular events, such as heart attacks and strokes, especially when unstable plaques rupture [43].

The pathophysiological mechanisms underlying periodontitis and other chronic conditions like rheumatoid arthritis, diabetes, and CVD are often similar, involving the alteration of immune regulation, oxidative stress management, and the transition from acute to chronic inflammation. Pro-inflammatory mediators play a crucial role in driving bone resorption, periodontal attachment loss, and the deterioration of bone and soft tissue, which are hallmark features of periodontitis [47].

According to Marcenes *et al.* (2013) [48], severe periodontitis was the sixth most prevalent health condition globally. The outcomes of the systematic review Trindade *et al.* (2023) [49] highlight that periodontitis remains a critical global public health concern, with an overall preva-

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lence of approximately 62% in dentate adults, based on studies conducted between 2011 and 2020. The prevalence of moderate to severe periodontitis was 53.2%, while severe cases accounted for 23.6% [41]. With the continuous rise in global population and life expectancy, the prevalence of periodontal conditions is expected to increase. However, it is crucial to emphasize that aging alone does not directly cause pathological periodontal attachment loss in otherwise healthy elderly individuals [42].

Recent systematic reviews have mapped 56 systemic conditions potentially linked to PDs, which represent nearly 2% of diseases indexed in the MeSH vocabulary [50]. One of the most significant findings is the association between periodontitis and CVD. In particular, periodontitis is strongly linked with coronary heart disease, cerebrovascular disease, and increased cardiovascular mortality. Notably, individuals with periodontitis are at an elevated risk for these cardiovascular issues, independent of other known confounders [51]. The recognition of a potential link between oral health and systemic diseases has led to several studies investigating the impact of periodontal interventions on improving or preventing various systemic conditions. Observational studies have been conducted to explore the pathophysiological connections between PD and overall health, with growing interest in the role of oral health in preventing broader health issues [52,53]. Periodontitis shares several pathological pathways with CVD, especially in terms of systemic and local inflammation. The development of periodontitis is driven by three key factors: the presence of a pathogenic microbial ecosystem, the host's acute inflammatory and immune response, and the failure of these responses to resolve the infection, which contributes to a self-perpetuating cycle of tissue damage. As periodontitis progresses, systemic inflammation increases, but effective periodontal therapy has been shown to significantly reduce both clinical signs of disease and systemic inflammatory markers [54].

Inflammation in periodontitis is characterized by the activation of immune components involved in acute responses, and if this inflammation transitions into a chronic state, it disrupts immune tolerance, potentially causing damage to tissues, organs, and cells, thereby increasing the risk for various chronic diseases [55]. Chronic systemic inflammation, in particular, is a known contributor to conditions like atherosclerosis, cancer, obesity, and neurodegenerative diseases, all of which are strongly associated with cardiovascular risk. Moreover, inflammation impairs immune function, which can lead to increased susceptibility to infections and other conditions, such as autoimmune diseases [56,57].

Interestingly, periodontitis patients exhibit higher levels of antibodies that cross-react with cardiovascular tissue antigens. This immune response can trigger the production of pro-inflammatory cytokines and pro-thrombotic mediators, with higher serum IgG levels against *P. gingivalis*, a periodontal pathogen, being associated with both periodontitis and CVD [58]. Peripheral blood neutrophils, key players in the body's defense against infection, are found to be hyperresponsive in periodontitis, overproducing ROS and proteases, which contribute to tissue damage [59]. The hyperactivation of neutrophils is associated with an amplified inflammatory response in periodontal tissues, exacerbating damage to both oral and systemic health. While reactive oxygen species (ROS) are crucial for microbial defense and cell signaling, their excessive production can lead to cellular and tissue damage, contributing to disease progression [60]. In fact, ROS plays a dual role in periodontitis contributing to pathogen neutralization while also posing a risk to host tissues when overproduced. Recent studies indicate that excessive ROS generation in periodontitis leads to tissue damage, which may contribute to the pathogenesis of systemic diseases, including CVD [59,61].

Moreover, severe periodontitis has been associated with dyslipidemia, particularly lower levels of high-density lipoprotein, which is known to protect against CVD [62]. As immune responses become inefficient at resolving the infection, they evolve into chronic inflammation that can spread throughout the body, contributing to systemic conditions like CVD. This chronic, unresolved inflammation may also lead to endothelial dysfunction, a key factor in atherosclerosis development. The chronic inflammation that characterizes periodontitis can also promote the formation of atheromas within the arteries, and it compromises the integrity of arterial plaques, making them more prone to rupture and causing thromboembolic events. Research suggests that periodontal bacteria, such as *P. gingivalis*, *Tannerella forsythus*, and *Prevotella intermedia*, may enter the bloodstream through damaged periodontal tissues. These bacteria have been shown to invade cardiovascular tissues, including the aortic and coronary arteries, and were detected in human carotid atheromas. This suggests a direct pathway through which periodontal infections may exacerbate CVD [62,63]. The fimbriae of *P. gingivalis*, an important virulence factor, facilitates the bacteria's entry into host cells and promote atherothrombotic lesions in experimental models [64]. The presence of *P. gingivalis* and other oral bacteria in atheromas can also activate platelets, promote clot formation and exacerbating the inflammatory response, which contributes to the progression of atherosclerosis and increases the risk for cardiovascular events [63,64].

One key area of interest is the genetic overlap between periodontitis and CVD. A study has suggested that genetic variants associated with aberrant inflammatory responses may predispose individuals to both conditions [65]. Specific genes, such as CDKN2B-AS1 (ANRIL), PLG, and CAMTA1/VAMP3, have been linked to higher CRP levels, a marker of systemic inflammation, and an overgrowth of periodontal pathogens in the subgingival space, both of which are associated with increased cardiovascular risk [65].

The pathophysiological mechanisms underlying periodontitis and CVD share significant commonalities, particularly in their inflammatory pathways. While the link between these conditions is well-established, more research is needed to fully understand the precise interactions between periodontal health and cardiovascular risk, including the role of oral bacteria in systemic inflammation and the potential for targeted treatments.

### *The Mechanisms Linking PD to Atherosclerosis*

The oral cavity hosts a diverse microbial community that plays a crucial role in maintaining oral and systemic health. Disruptions in this microbiome can lead to oral diseases, such as periodontitis, and have been linked to systemic conditions, including CVDs. A comprehensive review highlighted associations between the oral microbiome and various systemic diseases, emphasizing the importance of maintaining oral microbial balance [43]. Research has identified specific oral bacteria within atherosclerotic plaques, suggesting a direct microbial contribution to plaque formation. A study utilizing 16S rRNA gene sequencing found common bacterial phylotypes in oral, gut, and atherosclerotic plaque samples from individuals, indicating that oral bacteria may translocate and influence atherogenesis [66].

The three proposed mechanisms by which oral bacteria contribute to CVDs include systemic inflammation, direct bacterial invasion, and molecular mimicry (Fig. 1). First, systemic inflammation occurs when oral pathogens induce an immune response that extends beyond the oral cavity, leading to endothelial dysfunction and promoting the development of atherosclerosis. Next, direct bacterial invasion involves the translocation of oral bacteria into the bloodstream, where they can adhere to vascular tissues and contribute to the formation of atherosclerotic plaques. Finally, molecular mimicry arises when structural similarities between bacterial antigens and host tissues trigger autoimmune responses, resulting in vascular damage and the progression of atherosclerosis [67].

There is substantial evidence that oral bacterial species can enter the bloodstream and cause bacteremia, which has been observed following routine daily activities such as tooth brushing, flossing, chewing, or biting into an apple [68,69]. However, bacteremia has been more frequently studied in the context of professional dental interventions, including tooth polishing, scaling, extractions (both simple and surgical), and periodontal probing. A systematic review has linked the risk of bacteremia to periodontal health status, suggesting a greater likelihood of bacteremia in individuals with gingival inflammation [70]. Periodontal therapy leads to a reduction in platelet hyperreactivity in patients with periodontitis, indicating potential systemic benefits of this intervention. The study results demonstrate that post-therapy, there is a significant decrease in platelet activation markers, including PAC-1 binding, and P-selectin, as well as the formation of platelet-leukocyte complexes in response to *P. gingivalis*. These findings suggest that improving oral health may play a crucial role in reducing thrombotic risk and could potentially contribute to the prevention of cardiovascular events in at-risk patients [71]. Despite some methodological limitations in certain studies, the overall body of evidence supports the notion that bacteremia arises from both everyday activities and dental procedures and that it is more prolonged, more frequent, and involves more virulent bacteria in individuals with periodontitis.

Molecular evidence, including DNA, RNA, and antigen traces from oral bacterial species primarily periodontal pathogens have been identified in atherothrombotic tissues. Studies have attempted to correlate the presence of these bacteria in atherothrombotic plaques with other biological samples, such as subgingival plaque or serum, from the same individuals, indicating a stronger likelihood of such a correlation in periodontitis patients [72]. Viable *P.gingivalis* and *Aggregatibacter actinomycetemcomitans* have been cultured from atherothrombotic tissue [73,74].

Extensive research utilizing animal models has provided compelling evidence of the role of *P. gingivalis* in the pathogenesis of atherosclerosis. Studies in apolipoprotein E-deficient (ApoE$^{-/-}$) mice have demonstrated that systemic infection with *P. gingivalis* accelerates the development of atherosclerotic lesions, promotes macrophage infiltration, and enhances pro-inflammatory cytokine expression within vascular tissues [75]. Additionally, intravenous administration of *P. gingivalis* in murine models resulted in increased intimal hyperplasia, vascular smooth muscle cell proliferation, and enhanced lipid deposition in the aortic walls, further supporting its role in atherogenesis [76]. In porcine models, bacteremia with *P. gingivalis* has been linked to aortic and coronary artery lesions, indicating a potential translational impact on human cardiovascular pathology [77]. Additionally, in our previous study on mice with induced PD, we observed elevated levels of *P. gingivalis* mRNA in the cardiac tissues of PD mice, providing further evidence of bacteremia and the subsequent impact of *P. gingivalis* on CVD [78].

Collectively, these findings underscore the complex interplay between *P. gingivalis* and host cellular mechanisms, highlighting the bacterium's role in promoting atherosclerosis through direct vascular invasion, immune modulation, and induction of oxidative stress. Systemic inflammatory markers have been linked to periodontitis. Patients with periodontitis exhibit significantly elevated levels of CRP compared to healthy individuals, and CRP levels are further increased in those with both periodontitis and CVD. Notably, periodontal therapy has been shown to significantly reduce CRP levels while also improving cardiovascular health markers [79].

Recent studies have provided further evidence of the systemic inflammatory burden associated with periodonti-

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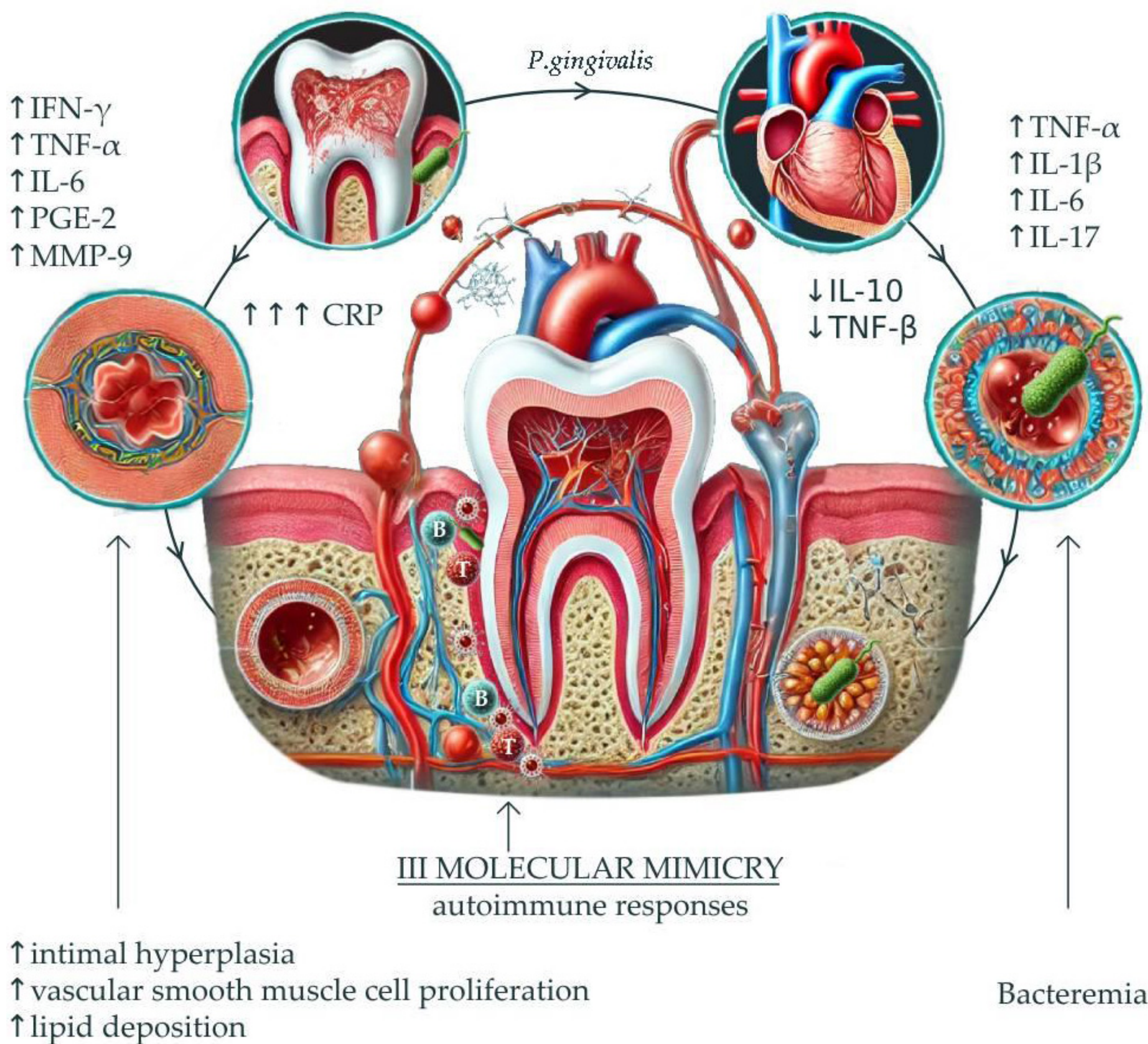


**Fig. 1. The Mechanisms Linking PD to Atherosclerosis.** I. Systemic Inflammation: Oral pathogens trigger an immune response, leading to elevated levels of IFN-$\gamma$, TNF-$\alpha$, IL-6, Prostaglandin E2 (PGE-2), MMP-9, and CRP. This systemic inflammation extends beyond the oral cavity, contributing to endothelial dysfunction, characterized by intimal hyperplasia, vascular smooth muscle cell proliferation, and lipid deposition within the arterial walls key processes in atherosclerosis development. II. Direct Bacterial Invasion: *Porphyromonas gingivalis* and other oral bacteria can translocate into the bloodstream, leading to bacteremia. These bacteria adhere to vascular tissues, promoting atherosclerotic plaque formation by upregulating pro-inflammatory cytokines (TNF-$\alpha$, IL-1$\beta$, IL-6, IL-17) and downregulating anti-inflammatory cytokines (IL-10, TGF-$\beta$). III. Molecular Mimicry: Structural similarities between bacterial antigens and host tissues can trigger autoimmune responses mediated by T and B lymphocytes. This immune cross-reactivity induces vascular damage, further accelerating atherosclerosis progression. Artwork: original, created by the authors using Adobe Illustrator (v.2024).

tis, particularly concerning elevated fibrinogen levels. A study by Mattila *et al*. (2002) [80] demonstrated that individuals with periodontitis exhibit higher plasma fibrinogen concentrations compared to healthy controls. Following periodontal treatment, a significant reduction in fibrinogen levels was observed, suggesting a direct link between periodontal inflammation and systemic fibrinogen concentrations [80].

Genetic studies suggest shared susceptibility loci between periodontitis and CVD. The highly pleiotropic CDKN2B-AS1 locus (chromosome 9p21.3), associated with coronary artery disease, ischemic stroke, type 2 diabetes, and Alzheimer's disease, has also been consistently linked to periodontitis [81,82]. These findings suggest a common mechanistic or immunological basis linking periodontitis and CVD, potentially driven by genetic variants

affecting inflammatory pathways. Another possible mechanism linking periodontitis to the development of atherosclerosis is the elevated level of homocysteine. Homocysteine, as one of the most important biomarkers in CVD, also plays a significant role in the pathogenesis of PD [83]. Notably, hyperhomocysteinemia is considered a risk factor for atherosclerosis and other CVD, as it damages the endothelium of blood vessels, contributes to oxidative stress and endothelial dysfunction, and facilitates the accumulation of cholesterol and inflammatory cells. Additionally, it increases platelet aggregation and blood coagulation, potentially leading to thrombus formation. Furthermore, hyperhomocysteinemia promotes inflammatory processes by stimulating pro-inflammatory cytokines, contributing to the progression of vascular lesions, and inducing LDL cholesterol oxidation, thereby increasing the likelihood of atherosclerotic plaque formation [84,85]. In our study using a cystathionine $\beta$-synthase-deficient mouse model, we demonstrated a direct link between hyperhomocysteinemia and the development of PD, identifying it as a critical biomarker for its diagnosis [83]. This finding suggests a potential mechanistic pathway through which PD and atherosclerosis may be interconnected via elevated homocysteine levels.

### *Epidemiological Evidence*

Epidemiological studies provide strong evidence that patients with periodontitis exhibit significant endothelial dysfunction, as assessed by flow-mediated dilation, increased arterial stiffness, greater carotid intima-media thickness, and elevated arterial calcification scores (Table 1, Ref. [86–91]). Imaging data from the ATHEROREMO-IVUS study suggest an association between high levels of antibodies against periodontal pathogens and a reduced extent of positive atheromatous plaque remodeling [86].

There is substantial epidemiological evidence indicating a positive association between periodontitis and coronary heart disease. A systematic review identified multiple case-control and cohort studies demonstrating an increased risk of a first coronary event in patients with clinically diagnosed or severe periodontitis compared to those without periodontitis or with milder forms of the disease [87,88]. Relative risk estimates vary across studies depending on population characteristics and definitions of periodontitis (Table 1).

A similar association has been observed between periodontitis and cerebrovascular disease. Epidemiological studies suggest that individuals with PD have an increased risk of ischemic stroke. A large-scale cohort study found that individuals receiving regular dental care had a reduced risk of stroke, highlighting the protective effect of oral health maintenance (Table 1) [89]. Additionally, an analysis of data from the Atherosclerosis Risk in Communities (ARIC) study found that individuals with periodontitis had more than double the risk of cardioembolic and thrombotic stroke compared to periodontally healthy individuals (Table 1) [92].

Limited but consistent evidence supports an association between periodontitis and an increased prevalence and incidence of peripheral artery disease (PAD). Meta-analyses and large population-based studies have demonstrated a positive association between periodontitis and PAD, with clinical attachment loss and radiographic bone loss severity correlating with lower Ankle-Brachial Index values (Table 1) [90]. However, no studies have directly evaluated the relationship between periodontitis and major adverse limb events.

Multiple studies have reported a positive association between periodontitis and atrial fibrillation (AF). Large-scale epidemiological analyses provide robust evidence supporting this link. A nationwide cohort study utilizing data from the Korean National Health Insurance Database found that individuals with periodontitis had a 21% increased risk of developing AF compared to those without periodontitis (hazard ratio, HR = 1.21, 95% CI [1.12; 1.31]) [91]. Furthermore, participants who improved their periodontal health exhibited a reduced risk of AF (HR = 0.89, 95% CI [0.83; 0.96]), suggesting that periodontal treatment may have a protective effect against CVD (Table 1).

The biological mechanisms underlying this association involve systemic dissemination of periodontal pathogens such as *P. gingivalis*, triggering immune responses that lead to pro-inflammatory cytokine production, endothelial dysfunction, and hypercoagulability. These pathways contribute to atrial structural remodeling and an increased propensity for arrhythmic events. Given the accumulating evidence, periodontal health may represent a modifiable risk factor for atrial fibrillation, emphasizing the importance of integrating oral health strategies into CVD prevention programs.

Currently, scientific evidence remains limited regarding CVD serves as a risk factor for the onset or progression of periodontitis. Among studies examining the association between periodontitis and secondary cardiovascular events, findings are inconsistent. A smaller study reported a potential link (HR = 2.8, 95% CI [1.2; 6.5]) with recurrent cerebrovascular events [93]. Further research is warranted to clarify the bidirectional relationship between periodontitis and CVD.

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*Interventional Studies: Does Treating PD Impact Cardiovascular Risk?*

Epidemiological research strongly suggests an independent link between periodontitis and CVD, even after accounting for known confounders. However, substantial intervention studies are needed, with long-term follow-ups that extend from the onset of subclinical CVD to the occurrence of clinical events, as well as very large sample sizes. Few studies in literature meet these requirements.

A study by de Oliveira *et al.* (2010) [94] followed 11,869 participants (mean age: 50) from the Scottish Health Survey for an average of 8.1 years to investigate the association between oral hygiene, inflammatory markers, and incident CVD. The study recorded 555 CVD events, 170 of which were fatal. Participants with poor oral hygiene showed a higher risk of CVD and increased CRP and fibrinogen concentrations. Specifically, those who brushed their teeth less frequently had a 70% higher risk of CVD compared to those who brushed twice daily. Furthermore, infrequent brushing was linked to higher levels of both CRP and fibrinogen. This reinforces the connection between poor oral hygiene and increased CVD risk due to systemic inflammation (Table 2, Ref. [91,94–100]) [94].

Holmlund *et al.* (2017) [95] studied 5297 individuals receiving periodontal treatment at a specialized clinic. They compared data from baseline to one year after active treatment, defining poor treatment response as having >10% of sites with pocket probing depth (PPD) greater than 4mm and bleeding on probing (BoP) at 20% or more of the sites. Over a median follow-up of 16.8 years, 870 new CVD cases were observed. Those with poor responses (13.8% of the sample) had a significantly higher incidence of CVD (23.6%) compared to those who responded well to treatment (15.3%). Interestingly, the number of remaining teeth was a predictor of CVD risk, but this was more prominent in the group with poor treatment responses. This suggests that effective periodontal treatment may help reduce subclinical CVD progression (Table 2) [95].

Another large-scale study by Lee *et al.* (2015) [96], based on data from the Taiwanese National Health Insurance Research Database (NHIRD), involved 720,343 patients, 511,630 with periodontitis and 208,713 without it over a 10-year period. The study found the lowest rate of CVD events in those who received dental prophylaxis (0.11%/year) and the highest rate in untreated periodontitis patients (0.31%/year). The incidence of acute myocardial infarction was significantly lower in treated periodontitis patients compared to those who received no treatment (Table 2) [96].

Park *et al.* (2019) [14] analyzed data from 247,696 healthy adults aged 40 and older, who had no prior major cardiovascular events, and participated in an oral health screening program, over a median follow-up of 9.5 years. During this period, 14,893 major cardiovascular events occurred, with a 6.84% event rate over 10 years. Cardiovascular events were more frequent among individuals with PD, dental caries, or tooth loss. The study showed that regular dental care, such as annual visits for professional cleaning, reduced cardiovascular risk by 14%. Moreover, brushing teeth one additional time daily reduced cardiovascular event risk by 9% (Table 2) [14].

These findings highlight the importance of regular dental care in reducing the cardiovascular risks associated with PD, dental caries, and tooth loss. Regular dental visits were also linked to lower risks of stroke, overall mortality, peripheral artery disease, and ischemic heart disease. Furthermore, improved self-performed oral hygiene and periodontal treatments may help prevent hypertension and enhance the effectiveness of antihypertensive treatments [101]. However, Rodrigues *et al.* (2023) [97] found that nonsurgical periodontal therapy (NSPT), while beneficial for improving periodontal health and lowering CRP levels, did not reduce blood pressure in patients with refractory hypertension and periodontitis (Table 2).

NSPT has shown effectiveness in improving periodontal health and reducing markers of inflammation in patients with periodontitis or peri-implantitis. A meta-analysis by Orlandi *et al.* (2014) [98] found that periodontal therapy improved flow-mediated dilation by 6.64%, which is a measure of endothelial function (Table 2). Another systematic review, Teeuw confirmed that periodontal treatment improves the inflammatory and lipid profiles of individuals, particularly those with comorbidities like diabetes and CVD [102]. Additionally, other studies have demonstrated that periodontal treatment lowers HbA1c and fasting plasma glucose levels in diabetic patients [103,104].

Statins, commonly prescribed for their lipid-lowering effects, have also been studied for their potential in treating periodontitis due to their pleiotropic effects. These include reducing pro-inflammatory interleukins and enzymes like MMP-1 and MMP-3, which are linked to PD. Statins also lower the levels of Inducible Nitric Oxide Synthase (iNOS) and Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) while increasing osteoprotegerin levels in periodontal tissues [105,106]. While stations have shown promise in reducing inflammation, their systemic use has not been shown to improve the outcomes of NSPT. However, local administration of statins alongside NSPT has demonstrated additional benefits, improved clinical attachment, and reduced PPD, particularly with the use of simvastatin. Local statin administration is beneficial because it provides higher drug bioavailability at the target site with fewer side effects compared to systemic intake.

Although NSPT is widely studied and recognized as a standard approach for preventing CVD due to its standardization, it can trigger a significant acute-phase inflammatory response, especially after full-mouth treatments. Research by Lee *et al.* (2015) [96] found a lower acute myocardial infarction (AMI) risk in patients who received dental prophylaxis and a higher risk in both untreated peri-

**Table 1. Overview of selected epidemiological studies.**

| Study | Sample size | Key findings | Conclusion |
|---|---|---|---|
| Sen *et al*. [86] | 9666 patients (ARIC study, median follow-up: 15.7 years) | Periodontitis significantly increases ischemic stroke risk, doubling the likelihood of cardioembolic and thrombotic stroke. | Periodontitis is an independent risk factor for ischemic stroke, highlighting the role of regular dental care in risk reduction. |
| Ahn *et al*. [87] | 6155 adults (Korean cohort) | Periodontitis is associated with increased carotid intima-media thickness, arterial stiffness, and a higher risk of subclinical atherosclerosis. | Periodontitis contributes to early atherosclerosis development, emphasizing the need for oral health in CVD prevention. |
| Yang *et al*. [88] | Meta-analysis of 8 studies (N >10,000) | Periodontitis increases PAD risk (OR = 1.78, 95% CI [1.25–2.54]), with the strongest link in severe cases. | Periodontitis is a potential PAD risk factor, and systemic inflammation may contribute to vascular pathology. |
| Lu *et al*. [89] | NHANES 1999–2002 (6000+participants) | Clinical attachment loss is significantly linked to lower Ankle-Brachial Index (ABI), indicating increased PAD risk (OR = 2.2, 95% CI [1.2–2.4]). | Periodontitis may contribute to systemic vascular dysfunction, increasing PAD risk. |
| Chen *et al*. [90] | Nationwide Taiwanese cohort (≥100,000 participants) | Periodontitis was associated with a 31% increased risk of atrial fibrillation/flutter (HR = 1.31, 95% CI [1.20–1.43]). | Periodontitis may promote atrial remodeling and increase AF risk, highlighting potential cardiovascular benefits of early periodontal treatment. |
| Park *et al*. [91] | 1.3 million individuals (Korean National Health Insurance Database) | Patients with periodontitis had a 21% higher risk of developing AF (HR = 1.21, 95% CI [1.12–1.31]), while improved periodontal health lowers risk (HR = 0.89, 95% CI [0.83–0.96]). | Strengthens the link between periodontitis and AF, suggesting periodontal therapy may lower AF incidence. |

OR, odds ratio; HR, hazard ratio; CI, confidence interval; PAD, peripheral artery disease; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; NHANES, National Health and Nutrition Examination Survey.

**Table 2. Overview of selected intervention studies.**

| Study | Sample size | Key findings | Conclusion |
|---|---|---|---|
| de Oliveira *et al*. [94] | 11,869 (8.1 years follow-up) | Poor oral hygiene is associated with a 70% higher CVD risk, linked to increased CRP, fibrinogen, IL-6, and TNF-$\alpha$. | Poor oral hygiene promotes systemic inflammation and significantly increases CVD risk, highlighting the importance of regular oral care. |
| Holmlund *et al*. [95] | 5297 (16.8 years follow-up) | Poor periodontal treatment response is associated with higher CVD incidence (23.6% vs. 15.3%) and elevated IL-1$\beta$ and IL-6 levels correlate with disease severity. | Effective periodontal treatment may slow subclinical CVD progression. Reinforces the link between oral and cardiovascular health. |
| Lee *et al*. [96] | 720,343 (10 years follow-up) | Lowest cardiovascular event rate in patients receiving regular dental prophylaxis (0.11%/year), highest in untreated periodontitis patients (0.31%/year). Reduced IL-6 and CRP levels noted in treated individuals. | Regular dental prophylaxis is associated with a reduced risk of AMI. Preventative oral care is crucial for cardiovascular health. |
| Park *et al*. [91] | 247,696 (9.5 years follow-up) | Regular dental visits reduce CVD risk by 14%, and an additional daily brushing lowers risk by 9%, with decreased TNF-$\alpha$ and IL-6 levels. | Professional dental care and improved oral hygiene reduce cardiovascular risk, emphasizing daily brushing and prevention. |
| Rodrigues *et al*. [97] | Patients with resistant hypertension | NSPT improved periodontal health and reduced CRP, IL-6, and TNF-$\alpha$ but had no significant effect on blood pressure. | NSPT alone is insufficient for hypertension control in CVD patients but may help reduce systemic inflammation, suggesting the need for adjunctive therapies. |
| Orlandi *et al*. [98] | Multiple studies | Periodontal therapy improved endothelial function (FMD+6.64%) and reduced IL-6, CRP, and serum amyloid A levels. | Periodontal treatment improves vascular function and may aid atherosclerosis prevention, reinforcing the systemic benefits of oral health interventions. |
| Minassian *et al*. [99] | Large patient cohort | A transient rise in vascular event risk occurs within 4 weeks post-invasive dental treatment, with elevated IL-1$\beta$ levels but no long-term adverse effects. | Short-term cardiovascular risks of dental procedures are temporary, while long-term benefits outweigh initial risks. |
| Nordendahl *et al*. [100] | 51,880 AMI patients | Invasive dental treatments do not increase AMI risk, contradicting previous concerns, with no significant IL-6 or TNF-$\alpha$ changes. | Periodontal treatments are safe for CVD patients, emphasizing the importance of oral health without cardiac risk concerns. |

CRP, C-reactive protein; IL-1$\beta$, interleukin-1 beta; IL-6, interleukin-6; TNF-$\alpha$, tumor necrosis factor-alpha; FMD, flow-mediated dilation; AMI, acute myocardial infarction; NSPT, nonsurgical periodontal therapy; CVD, cardiovascular disease.

odontitis patients and those undergoing intensive periodontal treatments [99]. A study by Minassian *et al.* (2010) [99], based on U.S. Medicaid claims, observed an increased rate of vascular events during the first four weeks following invasive dental treatment. However, these risks subsided within six months. Despite the short-term risks, the long-term cardiovascular benefits of periodontal treatment likely outweigh the initial adverse effects (Table 2).

Lastly, a study by Nordendahl *et al.* (2018) [100], involving 51,880 patients with first-time AMI, found no increased incidence of AMI following invasive dental treatments within the preceding four weeks. This suggests that invasive periodontal treatments are safe, even for patients with established CVD (Table 2) [100].

The conclusion from many studies is that there is not enough evidence to determine the effect of periodontal therapy on preventing CVD, and more research is required before any solid recommendations can be made.

## Future Directions

While strong evidence suggests an association between PD and ASCVD, significant gaps remain in establishing causality, identifying precise mechanistic pathways, and determining the effectiveness of periodontal interventions in reducing cardiovascular risk. Addressing these limitations requires a multidisciplinary approach, integrating longitudinal clinical studies, standardized diagnostic frameworks, advanced imaging techniques, and artificial intelligence (AI) - driven analytics. One of the primary challenges in current research is the lack of longitudinal, high-quality randomized controlled trials (RCTs) that evaluate the direct impact of periodontal treatment on cardiovascular outcomes. Many existing studies are observational, making it difficult to distinguish whether PD contributes to ASCVD progression or merely shares common risk factors such as smoking, diabetes, and systemic inflammation. Future research should prioritize large-scale, long-term RCTs that assess whether periodontal therapy, including mechanical debridement, antimicrobial treatments, and host-modulating agents, results in measurable improvements in cardiovascular health. These trials should include comprehensive biomarker profiling (e.g., C-reactive protein, IL-6, TNF-$\alpha$) and advanced vascular imaging techniques (e.g., carotid intima-media thickness, coronary artery calcium scoring) to track disease progression more accurately.

Another key limitation is the heterogeneity in diagnostic criteria for both PD and ASCVD across studies. Variations in how PD severity is classified, based on clinical attachment loss, pocket depth, or inflammatory markers, lead to inconsistencies in study outcomes. Similarly, different cardiovascular studies use varying endpoints, such as coronary artery disease, stroke, or peripheral artery disease, making cross-study comparisons difficult. Future research must work towards establishing universal diagnostic criteria for both PD and ASCVD, integrating omics-based profiling (genomics, transcriptomics, and microbiomics) to improve disease classification and risk stratification. The oral microbiome's role in systemic inflammation and vascular health remains an area of active investigation. Recent studies suggest that specific periodontal pathogens, such as *P. gingivalis* and *Tannerella forsythia*, may directly influence atherogenesis through immune modulation and endothelial dysfunction. However, current research relies heavily on traditional microbiological techniques, which may not capture the full complexity of host-microbiome interactions. Future studies should employ metagenomic sequencing, machine learning (ML) - driven microbiome analysis, and multi-omics approaches to identify key microbial signatures linked to cardiovascular risk and explore their potential as therapeutic targets.

The integration of AI and ML in PD and cardiovascular research represents a promising direction. AI-driven predictive modeling can improve risk assessment by analyzing large datasets of periodontal and cardiovascular parameters, allowing for early detection of high-risk individuals. ML algorithms can also facilitate automated image analysis of periodontal structures and vascular plaques, enhancing diagnostic accuracy. Moreover, AI-powered biomarker discovery could help identify novel inflammatory mediators linking PD and ASCVD, guiding the development of personalized therapeutic strategies. Finally, interventional studies must evolve beyond traditional treatment approaches. While scaling and root planing remain the standard of care, emerging therapies such as host-modulation strategies, probiotics targeting dysbiotic oral microbiota, and adjunctive antimicrobial peptides warrant further exploration. In parallel, cardiovascular risk management should integrate periodontal screening and treatment protocols into routine clinical practice, particularly for high-risk patients with established ASCVD. Collaborative efforts between periodontists, cardiologists, and computational biologists will be essential in advancing translational research and optimizing patient outcomes. By addressing these research gaps through technological innovation, interdisciplinary collaboration, and standardized methodologies, future studies can provide definitive evidence on the role of PD in ASCVD progression and establish periodontal health as a critical component of CVD prevention strategies.

To enhance practicality, future work should reference broadly accepted guidelines and apply a consistent approach across studies. Clear diagnostic definitions, transparent reporting, and harmonized outcomes will facilitate comparisons of results and support stronger conclusions.

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## Discussion

### *Effectiveness of Periodontal Treatment in Reduction of Cardiovascular Risk*

Epidemiological studies have increasingly highlighted the potential connection between periodontitis and cardiovascular disease (CVD), independent of known confounders. This emerging evidence suggests that a focus on oral health could play a significant role in cardiovascular risk management. However, to deepen our understanding, future intervention studies must be designed with longer follow-up periods. Ideally, these studies should extend from the early stages of subclinical CVD through to clinical events and involve large sample sizes. Currently, there are only a limited number of studies that meet these robust criteria.

One notable study conducted by de Oliveira *et al.* [94] analyzed data from 11,869 men and women (mean age 50.0) who participated in the Scottish Health Survey, which aimed to represent the general population in Scotland. With an average follow-up of 8.1 years, this study explored the relationship between oral hygiene, incident CVD, and markers of inflammation and coagulation. The findings highlighted 555 CVD events, including 170 fatalities. Importantly, participants who reported poor oral hygiene faced an increased risk of CVD and exhibited higher levels of both CRP and fibrinogen. Specifically, those who brushed their teeth less frequently had a 70% higher likelihood of developing CVD compared to individuals who brushed twice a day. This correlation indicates that consistent oral hygiene practices can significantly influence systemic inflammation and, consequently, cardiovascular health. Additionally, a study by Holmlund *et al.* [95] examined 5297 individuals treated for PD at a specialized clinic. This research compared periodontal data at baseline and after active treatment, defining poor treatment response as having over 10% of sites with probing pocket depth (PPD) greater than 4 mm and a bleeding on probing (BoP) index of 20% or more one-year post-treatment. Over a median follow-up of 16.8 years, 870 new CVD cases were identified. Notably, those categorized as poor responders (13.8% of the sample) exhibited a significantly higher incidence of CVD (23.6%) compared to those who responded well to treatment (15.3%). These studies underscore the importance of maintaining good oral hygiene and effectively managing PD not only for oral health but also for cardiovascular health. As research in this area continues to develop, it may provide valuable insights into preventive strategies for reducing CVD risk.

Studies indicate that individuals with a higher number of remaining teeth who are poor responders to treatment may face an increased risk for CVD. Conversely, for those in the responder group, having fewer remaining teeth correlates with a higher risk for CVD. This highlights the critical role of effective periodontal care; while retaining teeth can be beneficial, it can also pose challenges when periodontal damage remains untreated. The depth of periodontal pockets is a significant factor in determining risk, as it affects both local and systemic health outcomes associated with periodontitis. Consequently, implementing successful periodontal treatments can positively influence the progression of subclinical CVD.

In a comprehensive study by Orlandi *et al.* [107], involving 720,343 patients 511,630 with periodontitis and 208,713 without over a decade-long follow-up from the Taiwanese National Health Insurance Research Database (NHIRD), 10,046 participants experienced CVD events. The findings revealed a yearly CVD incidence rate of 0.17% among all patients. Whereas for patients with periodontitis, those receiving dental prophylaxis had the lowest incidence rate (0.11% per year), while those without treatment faced the highest risk (0.31% per year; $p < 0.001$). In another study by Park *et al.* [14] of 247,696 healthy adults aged 40 and older, routine oral health screenings were found to effectively reduce CVD risk. During a median follow-up of 9.5 years, the occurrence of major cardiovascular events, including cardiac death, AMI, stroke, and heart failure, yielded a 10-year event rate of 6.84%. Notably, individuals suffering from PD, with more dental caries, or greater tooth loss experienced higher rates of cardiovascular events. Encouragingly, regular dental care and professional cleanings (at least once a year) can significantly reduce cardiovascular risk by 14%, even when accounting for other potential health factors. Additionally, increasing physical dental hygiene practices, such as brushing teeth one extra time per day, has been shown to lower the risk of cardiovascular events significantly by 9%. Although daily oral hygiene is vital for preventing periodontitis, it's essential to remember that effective oral care extends beyond tooth brushing alone. Professional cleaning by dentists or dental hygienists (nonsurgical periodontal therapy, NSPT) are crucial for removing subgingival deposits and mineralized plaques, which tooth brushing alone may not accomplish.

### *Controversial Effects of Periodontal Treatment in the Reduction of Cardiovascular Risk*

CRP is widely recognized as a marker of inflammation, and its roles extend beyond this function to include significant contributions to CVD. Various studies have investigated CRP's predictive capabilities concerning cardiovascular risk and the progression of atherosclerosis. The existing literature highlights a range of findings regarding the effect of periodontitis therapy on CRP concentrations, indicating an opportunity for further research due to a lack of large-scale, well-designed, long-term randomized controlled trials [107]. While CRP is a valuable tool, it is essential to acknowledge its limitations in cardiovascular risk assessment, as it may lack specificity. For example, de Souza *et al.* [108] conducted a non-randomized trial that revealed a significant decrease in CRP levels 60 days following peri-

odontal therapy in patients who started with levels above 3 mg/L. Similarly, Gupta *et al.* [109] observed reductions in CRP levels among both chronic and aggressive periodontal patients, with values declining from 3.03 ± 1.67 mg/L to 1.46 ± 1.67 mg/L, and from 3.09 ± 1.21 mg/L to 1.43 ± 1.21 mg/L, respectively, three months post-treatment. In contrast, Almaghlouth *et al.* [110] and Eickholz *et al.* [111] did not observe a significant reduction in CRP levels in patients who received periodontal therapy three months earlier. While the results vary, it is encouraging to see that periodontal therapy may play a significant role in lowering CRP levels, which could be associated with a reduced risk of cardiovascular events. This finding underscores the importance of pursuing further research to gain a deeper understanding of the relationship between periodontal treatment and systemic inflammation. By exploring this connection, we can enhance patient care and improve health outcomes.

The most commonly used adjuncts to periodontal therapy are antibiotics, which are primarily administered systemically. Their use has been linked to lower levels of CRP in patients with periodontitis. However, while systemic administration offers benefits, it also presents challenges, such as gastrointestinal issues, the development of bacterial resistance, and the need for frequent dosing to maintain adequate concentrations in periodontal pockets, since these drugs are metabolized by the liver and kidneys. In contrast, local drug administration provides an opportunity to mitigate these challenges. Locally administered antibiotics have shown promising results in improving periodontal health, although their long-term use is constrained by potential side effects. This limitation opens the door for the exploration of new therapeutic agents, including host modulators and natural substances. Ongoing research into these alternatives is crucial, and it would be valuable to assess their effectiveness in periodontal treatment and their potential influence on cardiovascular outcomes. Such investigations could lead to more effective and safer treatment strategies for patients with PD.

### *Treatment Safety and Temporal Risk*

Periodontal treatment can elicit short-lived inflammatory responses and, after invasive dental procedures, a transient increase in vascular event rates over ~4 weeks; these risks subside by six months [99]. In a national cohort, invasive dental treatments were not associated with an increased risk of a first acute myocardial infarction [100]. Conversely, routine dental prophylaxis is associated with lower cardiovascular event rates compared with no treatment [96]. Taken together, these data indicate that while short-term procedural risk exists, there is no evidence of sustained cardiovascular harm, and the long-term benefits of periodontal care are likely to predominate.

## Conclusions

The epidemiological association between PD and ASCVD is consistently documented across diverse populations. Nonetheless, critical uncertainties remain regarding the causal nature of this relationship and the extent to which it operates independently of shared risk factors such as smoking, diabetes mellitus, obesity, and socioeconomic determinants. Mechanistic insights encompassing microbial translocation, systemic immune dysregulation, endothelial dysfunction, and oxidative stress provide compelling biological plausibility. Furthermore, interventional studies demonstrate that periodontal therapy can ameliorate systemic inflammatory biomarkers and improve validated vascular surrogate measures.

However, despite these promising findings, conclusive evidence linking periodontal therapy to reductions in major adverse cardiovascular events is lacking. To advance the field, well-powered, long-term randomized controlled trials with standardized PD phenotyping, harmonized diagnostic criteria, and adjudicated ASCVD outcomes are imperative. The adoption of uniform definitions and outcome measures would enhance comparability across studies and enable stronger meta-analytic inferences.

From a clinical perspective, practitioners should remain cognizant of the potential bidirectional relationship between oral and cardiovascular health. While routine periodontal screening in individuals at elevated cardiovascular risk is not yet formally recommended, the integration of oral health into broader preventive cardiology frameworks represents a rational future direction. Importantly, although invasive dental procedures may induce transient systemic inflammatory responses and short-lived increases in vascular events, current evidence does not support a sustained elevation in long-term cardiovascular risk. On the contrary, the cumulative benefits of sustained periodontal health are likely to predominate and may contribute meaningfully to systemic well-being.

Taken together, the PD-ASCVD link underscores the necessity of interdisciplinary, patient-centered strategies that transcend traditional specialty boundaries and align with the broader concept of integrated care in contemporary medicine.

## Availability of Data and Materials

Not applicable.

## Author Contributions

DS, NP, MD, AM, KS, and SM made substantial contributions to the conception and design of the study, the acquisition, analysis, and interpretation of data. All authors were involved in drafting the manuscript and revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that any

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questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Ethics Approval and Consent to Participate

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## Conflict of Interest

The authors declare no conflict of interest.

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