AHA Scientific Statement

Periodontal Disease and Atherosclerotic Vascular Disease: Does the Evidence Support an Independent Association?

A Scientific Statement From the American Heart Association

The American Dental Association Council on Scientific Affairs Concurs With the Conclusions of This Report

Endorsed by the World Heart Federation

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***Abstract*—**A link between oral health and cardiovascular disease has been proposed for more than a century. Recently, concern about possible links between periodontal disease (PD) and atherosclerotic vascular disease (ASVD) has intensified and is driving an active field of investigation into possible association and causality. The 2 disorders share several common risk factors, including cigarette smoking, age, and diabetes mellitus. Patients and providers are increasingly presented with claims that PD treatment strategies offer ASVD protection; these claims are often endorsed by professional and industrial stakeholders. The focus of this review is to assess whether available data support an independent association between ASVD and PD and whether PD treatment might modify ASVD risks or outcomes. It also presents mechanistic details of both PD and ASVD relevant to this topic. The correlation of PD with ASVD outcomes and surrogate markers is discussed, as well as the correlation of response to PD therapy with ASVD event rates. Methodological issues that complicate studies of this association are outlined, with an emphasis on the terms and metrics that would be applicable in future studies. Observational studies to date support an association between PD and ASVD independent of known confounders. They do not, however, support a causative relationship. Although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent ASVD or modify its outcomes. **(*Circulation*. 2012;125:2520-2544.)**

Key Words: AHA Scientific Statements ■ atherosclerosis ■ coronary disease ■ infection ■ infectious disease ■ pathogenesis ■ periodontal disease

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on February 27, 2012. A copy of the document is available at http://my.americanheart.org/statements by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC Jr, Baddour LM, on behalf of the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation.* 2012;125:2520–2544.

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***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0b013e31825719f3**

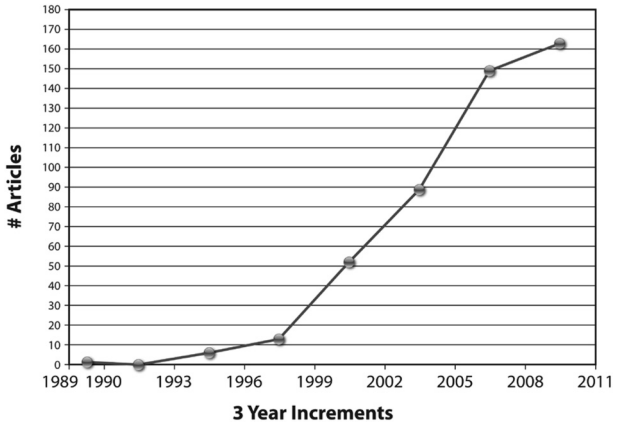

Figure 1. Periodontal/cardiovascular disease articles. The number of new peer-reviewed publications in English language journals on the topic of periodontal disease and all types of cardiovascular, peripheral vascular, and cerebrovascular diseases for 3-year periods is shown from 1989 (when the first article appeared) through 2010.

Well over a century ago, oral sepsis and dental extractions were proposed as causes of infection of cardiac tissues (ie, infective endocarditis).[1] This focal infection theory evolved over the following half century to become part of a larger concern about the linkage of focal odontogenic infection and a long list of diverse medical conditions remote from the mouth. An unprecedented surge in dental extractions ensued over several decades.[2–6] By the mid-20th century, lack of supporting scientific evidence tempered the focus on oral disease as a cause of systemic illness. That focus was revived ≈20 years ago after reports of a potential connection between chronic periodontal diseases (PDs) and atherosclerotic vascular disease (ASVD).[7,8] A dramatic increase in publications on this topic followed in 190 different journals (Figure 1).

Although many subsequent studies have suggested positive associations between these 2 diseases, others have not, particularly after adjustment for potential confounding variables.[9] At the same time, several potential mechanisms by which PD could cause systemic inflammation, promote atherogenesis, or incite cardiovascular catastrophes such as myocardial infarction (MI) or stroke have been proposed. Whether an independent, clinically significant association exists between the 2 disorders remains controversial.

This question has tremendous importance given the high incidences of both diseases, their economic costs to society, and the potential impact on public health if risk modification or therapeutic opportunities could be identified. The lack of consensus among experts and the confusion among healthcare providers and the public all suggest the need for a systematic review of the topic. Therefore, the present document was prepared to review the relevant pathophysiology, predominant theories, and investigative approaches and to assess the quality of available data that characterize the topic.

Methods

The American Heart Association's Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, which includes representatives from dental, infectious diseases, cardiology, and epidemiology communities, convened a writing group charged with assessing the weight and scope of evidence for an association or causality of PD and ASVD.

Table 1. Search Strategy and Criteria

The basic search strategy in *Ovid MEDLINE In-Process & Other Non-indexed Citations and Ovid MEDLINE* was as follows:

Database: Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1950 through July 31, 2011>

Search strategy:

1. exp Periodontal diseases/
2. exp Cerebrovascular disorders/
3. exp Cardiovascular diseases/
4. exp Cardiovascular system/
5. exp Periodontium/
6. exp Periodontics/
7. (1 or 5 or 6) and (2 or 3 or 4)
8. limit 7 to English language
9. limit 8 to (comment or letter or news or newspaper article)
10. 8 not 9
11. (periodont$ or tooth or teeth or gingiv$ or furcat$ or pericoroni$ or periapical or alveolar).af.
12. limit 11 to in process

From May 2008 to July 2011, we conducted a series of literature searches in the database Ovid MEDLINE In-Process & Other Nonindexed Citations and Ovid MEDLINE for English-language articles on the association between PD and any cerebrovascular, peripheral vascular, or cardiovascular disease, excluding infective endocarditis, Behçet syndrome, Stevens-Johnson syndrome, and Sjögren syndrome. The search strategy included a combination of Medical Subject Headings and key words (Table 1). The search covered the period of 1950 to July 2011 and included clinical studies, systematic reviews, animal studies, and articles of material importance to the subject of this report. Comments and letters, editorials, case reports, news items, and consumer health material were excluded.

The search produced 473 articles that met inclusion criteria. In addition, we identified 64 additional publications that met inclusion criteria from the reference lists of these 473 articles, for a total of 537 peer-reviewed publications. The majority appeared in the periodontal literature and other dental journals (61%) compared with the medical literature (39%). After review by writing group members for study design, relevance, and quality, only those specifically discussed in the present report were referenced.

Definitions and Prevalence of Cardiovascular Disease and PD

Cardiovascular Disease

ASVDs affect the heart and the blood vessels. Their major components, defined as diseases of the circulatory system by the *International Classification of Diseases, 9th Revision*, are as follows: (1) Ischemic heart disease, (2) cerebrovascular diseases, and (3) diseases of arteries, arterioles, and capillaries (also known as peripheral vascular disease). ASVD is a chronic process, with a progressive course over many years, but it can cause acute clinical events, including acute coronary syndromes (ACS), MI, and stroke.

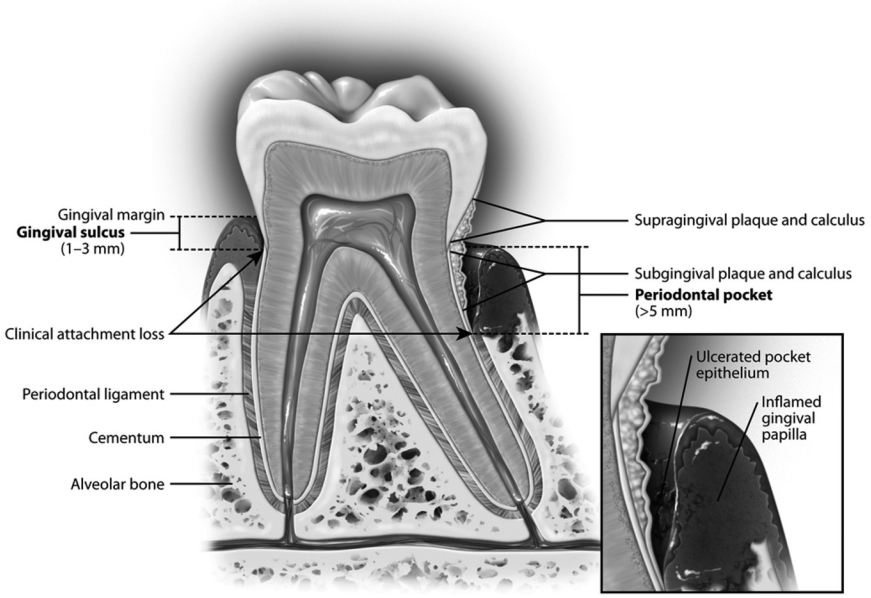

Figure 2. Periodontal anatomy in health and disease. Molar tooth with periodontal anatomy in health (**left side**) and with periodontal disease (**right side**). Note the greatly increased depth of the 1- to 2-mm gingival sulcus caused by loss of the gingival attachment to create a periodontal pocket of >5 mm; the inflamed and swollen gingival papilla and the loss of alveolar bone from the inflammatory response from subgingival plaque and calculus; and the presence of ulceration of the periodontal pocket mucosa and resultant loss of a mucosal barrier between the plaque bacteria and the increased gingival circulation. Courtesy of Anne Olson.

Atherosclerotic vascular diseases are the number 1 cause of death globally, accounting for ≈30% of all deaths worldwide. In the United States, despite declining trends in ASVD mortality since the early 1980s, ASVD remains the leading cause of disability and mortality, accounting for ≈1 in 3 deaths.[10]

The most common form of ASVD in the United States is ischemic heart disease, which caused more than half of all ASVD deaths in 2008.[10] Each year, an estimated 785 000 Americans have a new coronary event, and ≈470 000 experience a recurrent attack. It is estimated that an additional 195 000 silent first MIs occur annually. Additional ASVD burden presents as stroke: Each year, ≈795 000 people experience a new or recurrent stroke, and final data from 2008 indicate that stroke accounted for ≈1 of every 18 deaths in the United States.[10] Lower extremity peripheral artery disease, one of the most common manifestation of peripheral vascular disease, is estimated to affect 12% to 20% of the US population >65 years of age and ≈8 million Americans.[10] Overall, the spectrum of ASVD imposes a substantial cost to society. The total estimated direct and indirect costs of ASVD, including stroke, in the United States exceeded $298 billion in 2008.[10] A review of the pathophysiology of ASVD is beyond the scope of the present report.

Periodontal Disease

Periodontal diseases comprise a continuum of conditions involving inflammation of gingival tissues in response to dental plaque accumulation (Figure 2). These conditions may present with ("periodontitis") or without ("gingivitis") substantial inflammatory destruction of the supporting tissues, including gingival tissue, periodontal ligament, and alveolar bone.

Assessment of the global prevalence of PD across different populations has been impacted by substantial variation in the clinical criteria, such as bleeding on probing, pocket depth, and degree of attachment loss used to define the presence and severity of PD among studies. Grading systems for use in epidemiological studies have been proposed but have not been applied consistently. A lack of consensus on how to incorporate tooth loss data in prevalence estimates is an especially important limitation in elderly cohorts, because loss may occur because of dental disorders other than PD.[11]

A recent review of the epidemiological patterns of periodontitis reported a range in prevalence of severe periodontitis from 1% among 20- to 29-year-olds to 39% among individuals >65 years of age. Moderate forms of the disease were significantly more common in all populations.[12] On the basis of National Health and Nutrition Examination Survey 1999–2004 data, the prevalence of moderate to severe PD in the United States was 5% among those aged 35 to 49 years, 11% among those aged 50 to 64 years, 14% among those aged 65 to 74 years, and 20% among those aged >75 years.[13] The combined expenditure for periodontal and preventive dental services in the United States was estimated at $14.3 billion in 1999, whereas approximately $4.4 billion was spent for periodontal procedures.[14]

Periodontal Disease

Basic Periodontal Anatomy

Teeth are supported by a connective tissue attachment apparatus (periodontal ligament) that is partly inserted into the outer layer of the root surface (root cementum) and partly into bone of the maxillary or mandibular alveolar processes, and to a lesser extent by gingival tissues that surround the teeth (Figure 2). In states of periodontal health, the gingiva are firmly attached to the root surface at the level of the junction between tooth enamel and the root cementum. The highest level of the gingival margin is located between 1 and 3 mm coronal to the point where the gingiva attach to the tooth surface, which results in a shallow space around the periphery of the tooth called the *gingival sulcus*. Teeth and gingival epithelium that surround teeth form several different ecological environments, each suitable for colonization by a distinct group of microorganisms. The gingival sulcus is a unique ecological niche that is readily colonized by oral bacteria that form a biofilm, or dental plaque.

Pathophysiology

In periodontitis, bacterially induced inflammatory processes result in deepening of the gingival sulcus, which evolves into a

Table 2. Bacteriology of Dental Plaque

	Facultative	Anaerobic
Gram-positive cocci	*Streptococcus sanguis* *Streptococcus oralis* *Streptococcus mutans*	
Gram-positive bacilli		*Actinomyces naeslundii* *Actinomyces odontolyticus* *Actinomyces viscosus*
Gram-negative cocci	*Neisseria* species	*Veillonella* species
Gram-negative bacilli	*Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans* *Capnocytophaga* species *Eikenella corrodens* *Helicobacter pylori* *Chlamydophila pneumoniae*	*Porphyromonas gingivalis* *Fusobacterium nucleatum* *Prevotella intermedia* *Tannerella forsythia* *Selenomonas noxia* *Campylobacter rectus*
Spirochetes		*Treponema denticola* Other *Treponema* species
Methanogenic archaea		*Methanobrevibacter oralis*-like
Sulfate-reducing bacteria and archaea		*Desulfomicrobium orale* *Desulfovibrio*

periodontal pocket; apical migration of both the gingival attachment to the root surface and plaque biofilm; loss of connective tissue attachment and alveolar bone; and gingival recession.

Three clinical parameters are typically recorded in epidemiological studies of PD to assess prevalence: (1) Bleeding on probing, which reflects the presence of an inflammatory infiltrate in gingival tissues with loss of integrity of the sulcular epithelium; (2) pocket depth, which describes the deepening of the gingival sulcus from which dental plaque biofilm can propagate apically along the root surface; and (3) clinical attachment level, which reflects the amount of periodontal tissue loss. Thus, bleeding on probing and increased pocket depth are more indicative of current pathology, whereas attachment levels provide a cumulative measure of loss of support caused by the aggregate effects of pathogenetic factors such as PD and trauma. Clinical data are usually summarized as mean values of the above parameters or as measures of extent (ie, the percentage of sites in dentition that are affected by bleeding on probing, pocketing, or attachment loss) and severity (ie, the magnitude of loss of tissue support caused by disease, expressed in millimeters).

Other markers of periodontitis include evaluations of subgingival microbial colonization by selected periodontal organisms[15–18] and levels of serum IgG or IgA antibodies to selected periodontal bacteria.[19–26] A positive correlation between extent and severity of PD and increased levels of colonization by specific microbial species is widely accepted[27,28]; in contrast, the association between periodontal pathology and elevated antibody titers to putative pathogens is highly variable.[29] In some cases, high titers likely suggest the presence of a protective adaptive response, whereas in others, they reflect the severity of periodontitis.[30] This complicates the interpretation of data from studies that have exclusively used serological markers of periodontitis to study the association between periodontal infections and ASVD.

Microbiology of PD

A newly cleaned tooth surface is rapidly covered with a glycoprotein deposit referred to as a *pellicle*. The pellicle is derived from salivary constituents that are selectively adsorbed onto hydroxyapatite of the tooth surface. Microorganisms inhabit the pellicle above and below the gingival margin as supragingival and subgingival plaque. Unlike other bacterial ecosystems that inhabit continuously shedding epithelial surfaces, dental plaque develops on the nonshedding surface of teeth. It is a biofilm that consists of a complex microbial community embedded in a matrix of polymers of bacterial and salivary origin. The supragingival plaque is bathed by saliva, and the subgingival plaque is bathed by transudative fluid in the gingival sulcus.[31] In the presence of periodontitis, plaque in the periodontal pocket is bathed by exudative fluid, blood, or both.

The microbial composition of dental plaque differs above and below the gingival margin. Factors that influence the distinct pattern of microflora that inhabit each anatomic site include specific local surface receptors for bacterial adherence, oxygen tension, redox potential, pH, microbial coaggregation, and microbial interference. Microbial composition also varies by age, hormonal changes, diet, oral hygiene, and presence of caries and PD.

Initial ("primary") supragingival colonizers have particular affinity for constituents of the pellicle. These colonizers include *Streptococcus sanguis*, *Streptococcus oralis*, *Streptococcus mutans*, *Actinomyces naeslundii*, and *Actinomyces odontolyticus*. They provide attachment sites for interspecies adherence, supply substrates required for growth of other bacteria, and reduce oxygen tension to low levels that allow growth and survival of obligate anaerobes. The primary colonizers are followed by adherence of secondary colonizers, such as *Fusobacterium nucleatum*, which in turn coaggregate with later colonizers. Within a relatively short time, complex communities of gram-positive and gram-negative bacilli and cocci become embedded in an extracellular polymer matrix.[32] More than 500 distinct microbial species can be recovered from dental plaque (Table 2).[33] Bacterial counts above the gingival margin on a single tooth surface can exceed 10^9 bacteria per gram.[34] Below the gingival margin, the number of bacteria ranges from 10^3 in a healthy, shallow sulcus to $>10^8$ in

a periodontal pocket.[35] Many of the microorganisms found in subgingival plaque do not grow in culture.[36]

In healthy mouths, the most common organisms detected in subgingival plaque include *A naeslundii*, *S sanguis*, *S oralis*, *Veillonella parvula*, *A odontolyticus*, and *F nucleatum*.[33,37] In the presence of gingivitis, gram-negative microaerophilic bacilli and gram-negative anaerobic bacilli predominate in the subgingival flora. Subgingival microflora in gingivitis represent a transition between that associated with health and periodontitis,[38] in which subgingival microflora shifts from being predominately gram-positive to an increased number of obligate anaerobic gram-negative organisms, such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Selenomonas noxia*, as well as *Campylobacter rectus*, *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, and *Prevotella intermedia*, and spirochetes.[35–41] Other microorganisms found in PD include *Chlamydophila pneumoniae*[42]; *Mycoplasma*[43,44]; *Helicobacter pylori*[45–47]; candida[48–51]; Epstein-Barr virus, cytomegalovirus, and herpesviruses[52–54]; ameba[55]; methane-producing microorganisms called *archaea*[56–59]; and sulfate-reducing bacteria and archaea.[60,61]

Epithelium in the gingival sulcus interacts with bacteria in the subgingival crevicular space, generating and transmitting signals between bacteria and adjacent immune cells.[62] This results in elaboration of proinflammatory cytokines and chemokines that are responsible for recruiting cells involved in innate and acquired immune response and the inflammatory process (dendritic cells, T and B cells, macrophages, and neutrophils).[63]

Several putative PD pathogens (*P gingivalis*, *A actinomycetemcomitans*, and *P intermedia*) attach to gingival epithelial cells and induce formation of membrane invaginations (receptor-mediated endocytosis), which surround and engulf bacteria.[64–66] Survival and multiplication of intracellular *P gingivalis* permits evasion of the immune system and possible dissemination via the bloodstream.[67]

Risk Factors for PD and Cardiovascular Disease

Risk factors associated with the development of PD include local, systemic, and genetic factors. Although several bacterial species are currently recognized as causally associated with periodontitis,[27] mere colonization of the subgingival niche by these species is not sufficient for disease to occur.[68] Instead, PD is thought to evolve from the stage of gingivitis, that is, a local inflammatory process without concomitant loss of periodontal tissue support that likely represents a stable, largely protective host response to periodontitis, an environment characterized by loss of connective tissue attachment and alveolar bone, influenced by detrimental environmental exposures and specific genetic predispositions that are likely important determinants of susceptibility.[11,69] These include poor oral hygiene; cigarette smoking; systemic conditions such as diabetes mellitus, osteoporosis, rheumatoid arthritis, and possibly obesity; and stress and poor coping behaviors.[69] In addition, a number of genetic polymorphisms have been variably associated with propensity for periodontitis and ASVD.[70]

Contributors to ASVD are similarly multifactorial and include a complex interplay between genetic, environmental, and lifestyle factors. The associated risk factors include those that cannot be changed, such as ethnicity, age, and family history of ASVD, and those that can be modified or controlled, including dyslipidemia, hypertension, tobacco smoke, excess body weight, physical inactivity, and diabetes mellitus. The role of these classic risk factors and their interaction with cellular and noncellular mechanisms in the slow process of atheromatous plaque development is clearly established, with unequivocal evidence that by intervening on these risk factors, one can impede or prevent the atherosclerotic process and its clinical manifestations. In addition to factors associated with long-term progression of atherosclerosis, including chronic inflammation, there are also "triggering factors" that are more acute and include increased inflammation and a cascade of hemostasis and thrombosis. These triggers may lead to atherosclerotic plaque rupture and thrombosis, resulting in vessel occlusion and acute clinical catastrophes such as MI or stroke.

Many prevalent risk factors with well-documented impact are shared by ASVD and PD and could confound a relationship between them. Increasing age, smoking, alcohol abuse, race/ethnicity, education and socioeconomic status, male sex, diabetes mellitus, and overweight or obesity are all factors associated with both ASVD and PD.[71,72]

The presence of potentially significant confounding effects is an important potential limitation in many studies because of the nature of their study design (observational studies).[73] A number of studies, although not the majority of them, have presented evidence that confounding factors could play a role in explaining, at least in part, the observed association between ASVD and PD. These factors include smoking and other lifestyle factors, ASVD risk factors, age, and education and other social indicators.[73–78] The role of smoking in the observed association between PD and cardiovascular disease outcomes is a critical one because smoking can play a role both as a confounder and as an effect modifier. Smoking is a major risk factor for both periodontal and cardiovascular disease, and smoking cessation is a critical component of health maintenance and prevention of many diseases, including ASVD and PD. Statistical adjustment for smoking in studies of the association between PD and ASVD does not preclude the possibility for residual confounding; however, recent evidence seems to indicate that the observed association between PD and ASVD may be independent of smoking. It has been shown, both in cross-sectional[79] and in longitudinal studies,[80,81] that PD and ASVD are associated in never-smokers as well.

Pathogenic Mechanisms Proposed as Links Between Cardiovascular Disease and PD

Several pathophysiological pathways have been proposed as potential links between PD and ASVD. These pathways involve both direct and indirect interactions between periodontal pathogens and the endothelium or other mechanisms that impact the atherosclerotic process.

Indirect Mechanisms: Systemic Inflammation

Atherosclerosis may begin during childhood, with initial infiltration of the endothelium with fatty substances, and progresses over many decades. Chronic, quiescent atheromatous plaque can transition to a more dangerous state in which its vulnerability to rupture is increased. Plaques that contain a

soft atheromatous core are unstable, and their rupture will expose highly thrombogenic contents to blood, with activation of thrombosis and ensuing ACS, MI, or stroke.[82] Major determinants of increased plaque vulnerability are size and consistency of the atheromatous core and both thinning and inflammation of the fibrous cap covering the core. Such inflammation manifests as infiltrates of monocytes/macrophages, T cells, and neutrophils within the cap tissues,[82] as well as by increased circulating markers of inflammation in the blood. The link between ASVD and inflammatory mediators in blood is well established, with consistent associations between levels of systemic inflammatory markers and increases in clinical events such as MI and nonhemorrhagic stroke, and in surrogate markers such as increased carotid intima-media thickness (cIMT).[83]

Systemic inflammation can be measured with several inflammatory markers. A well-studied inflammatory marker is C-reactive protein (CRP). More than a dozen prospective epidemiological studies of individuals with no prior history of ASVD have demonstrated that a single nonfasting measure of CRP is a predictor of future vascular events, including MI, stroke, peripheral arterial disease, and sudden cardiac death.[84] CRP is an independent predictor of future cardiovascular events that may add prognostic information to lipid screening, the metabolic syndrome, and the Framingham risk score.[85,86]

Additional inflammatory markers associated with cardiovascular disease include lipoprotein-associated phospholipase A2,[87] matrix metalloproteinases and tissue inhibitors of matrix metalloproteinase,[88] myeloperoxidase,[89] and fibrinogen.[90,91] Other inflammatory markers (eg, interleukin 6 [IL-6], soluble intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, and soluble CD40 ligand) have been shown to be elevated among those at increased vascular risk, albeit to a lesser magnitude than CRP.[85]

Periodontal inflammation is similarly associated with increased systemic inflammatory markers, including CRP, tumor necrosis factor-α, IL-1, IL-6, and IL-8.[92–95] Systemic inflammation is associated with cellular activation that involves cellular adhesion molecules, toll-like receptors, matrix metalloproteinase, and nuclear factor-κB activation. The resulting interplay between endothelium, monocytes, and platelets might be proatherogenic,[96–99] contributing indirectly to atherogenesis or to adverse cardiovascular outcomes related to atheromatous plaque rupture in subjects with periodontitis.[96,97,100] There are also data to suggest that the inflamed periodontium produces CRP locally, but to what extent locally produced CRP accounts for higher circulatory CRP levels in periodontitis has not been determined.[101,102]

Indirect Mechanisms: Mimicry

Molecular mimicry has been raised as a possible mechanism linking periodontal infection with atherosclerosis. Molecular mimicry is thought to occur when sequence similarities between foreign and self-peptides produce cross-activation of autoreactive T or B cells that can lead to tissue pathology or autoimmunity.[103] Cross-reactive autoantibodies to periodontal bacterial lipopolysaccharides and heat shock proteins have been identified[96–99] and invoked as a potential explanation for the putative relationship between PD and ASVD.[104] Expression of host protective heat shock proteins (HSPs) such as HSP60 on endothelial cells may be induced by a variety of factors, including cytokines and shear stress, and antibodies to HSP60 have been associated with higher morbidity and mortality from atherosclerotic ASVD.[105] Proponents of molecular mimicry as a link between PD and ASVD suggest that endothelial damage may be aggravated by an immune response to bacterial HSP, such as the molecular chaperone GroEL, present in *P gingivalis* and other periodontopathic bacteria.[104] Host antibodies directed against *P gingivalis* GroEL have cross-reactivity with HSP60 on human endothelial cells.[106] Moreover, cross-reactive T cells have been found in diseased periodontal tissue, peripheral blood, and atherosclerotic lesions.[107] Studies in experimental animals lend further support to the hypothesis that cross-reactivity of the immune response to bacterial HSP has a role in accelerating atherosclerosis. In murine models, atherosclerosis is augmented by immunization with recombinant HSP.[108] Apolipoprotein E–deficient mice infected with *P gingivalis* have accelerated development and progression of atherosclerosis compared with control mice.[109–111]

Direct Mechanisms: Bacteremia and Vascular Infection by Periodontal Pathogens

Adults harbor more than a billion bacteria in their mouths. Although the flora varies in different oral regions, the area of greatest potential relevance to atherosclerosis is the periodontal pocket. The total surface area of the pockets in patients with periodontitis is estimated to be between 8 and 20 cm^2, and regions of ulceration in the pocket place the bacterial biofilm in close proximity to the circulation.[112]

Bacteremia that originates from the mouth is a common event that can occur during chewing and tooth brushing. It potentially occurs multiple times per day in individuals with some degree of gingivitis and periodontitis.[113] A comprehensive search of the literature provides a list of >275 bacterial species that have been identified in blood cultures after routine daily events or dental procedures.[114,115] The nature of the bacterial species that enter the circulation reflects the resident flora at that location, from those that colonize the supragingival region down to the deep subgingival sulcus. Viridans group streptococci represent a significant proportion of the flora around teeth, particularly in dental biofilm that grows above the gingival crest (gum line). In contrast, deeper periodontal pockets harbor other microbes, such as anaerobic microorganisms and gram-negative species. A strong association between the incidence of bacteremia after tooth brushing and 3 indices of oral hygiene and gingival disease (plaque, calculus, and gingival bleeding) has been demonstrated; moreover, these associations strengthen as the indices increase in severity.[113] These data strongly suggest that the gingival sulcus is the main source and portal to the bloodstream for oral bacterial species detected in the blood.[114–118]

From there, periodontal organisms circulate in the bloodstream either within phagocytic cells or extracellularly and subsequently are deposited in an atheromatous plaque. Common PD pathogens including *P gingivalis* adhere to and invade various human vascular cells in culture.[119–121] Infection of aortic endothelial cells by *P gingivalis* induces a procoagulant response that might contribute to a vasculopathic role.[121]

Periodontal bacterial components have been demonstrated in human atheromatous plaques at various sites (Table 3). For

Table 3. Microbiology of the Atherosclerotic Plaque

Evidence	Microorganisms	References
1. Seroepidemiological data	*Chlamydophila pneumoniae*	122–126
	Mycoplasma pneumoniae	127
	CMV	122, 128–130
	HSV	131
	Hepatitis B virus carriers	132
	Hepatitis C virus	133
2. Immunocytochemistry in tissue	*Chlamydophila pneumoniae*	122, 134–136
	CMV, HSV type 1	135, 136
	Porphyromonas gingivalis, Streptococcus sanguis	136
3. Electron microscopy in tissue	Herpes virus	137
	Mycoplasma pneumoniae	138
	Chlamydophila pneumoniae	122
4. Microbial nucleic acid in tissues by means of PCR amplification	Multiple bacterial species (5–22 species/specimen) that included staphylococci, streptococci, *Proteus vulgaris, Klebsiella pneumoniae*	139
	Periodontal pathogens (*Porphyromonas gingivalis, Tannerella forsythia, Aggregatibacter actinomycetemcomitans, Prevotella intermedia*)	140
	Chlamydophila pneumoniae	122, 134, 139, 141, 142
	Helicobacter pylori	142
	HSV	143
	CMV	144–146
	Fungi	147
5. In situ hybridization in atheroma	*Mycoplasma pneumoniae*	138
	Chlamydophila pneumoniae	122
	Herpes simplex virus	143, 148
6. Experimental animal models	CMV	149, 150
	HSV	151
	Chlamydophila pneumoniae	152, 153
	Influenza A virus	154
	Porphyromonas gingivalis	155
	Mycoplasma pneumoniae	153
7. Cell cultures that implicate a variety of microorganisms in the induction of atherosclerosis		119, 156, 157
8. Recovery of viable microorganisms in cultures of human atheroma	*Chlamydophila pneumoniae*	122, 158

The microorganisms that have been implicated in the pathogenesis of atherosclerosis include bacteria (eg, dental plaque microorganisms such as *Porphyromonas gingivalis*; *Chlamydophila* [formerly *Chlamydia*] *pneumoniae*; and *Helicobacter pylori*), viruses (eg, herpes simplex virus-1; cytomegalovirus; hepatitis B and C viruses; and influenza A virus), and fungi. The evidence for specific microorganisms is derived from the studies cited above.

CMV indicates cytomegalovirus; HSV, herpes simplex virus; and PCR, polymerase chain reaction.

example, in a single-center study of 35 patients undergoing valve replacement for regurgitant lesions and 27 patients undergoing thoracoabdominal aortic aneurysm repair, cariogenic *Streptococcus mutans* was detected in 69% of heart valves and 74% of atheromatous plaque specimens.[108] The frequency of detection of other bacteria was much lower. Fiehn et al[159] failed to isolate viable oral bacteria from atheromas of 79 surgical specimens of carotid or femoral arteries but did detect DNA of periodontal pathogens. Similarly, Haraszthy et al[140] found that 80% of 50 carotid endarterectomy specimens were positive in 1 or more of the polymerase chain reaction assays for *A actinomycetemcomitans*, *T forsythia*, *P gingivalis*, and *P intermedia*. In 33 patients with advanced chronic periodontitis scheduled for carotid endarterectomy, bacterial DNA was extracted from subgingival plaque samples and carotid atheromas.[160] Bacterial DNA was detected in 31 of 33 endarterectomy specimens; however, none of the samples tested positive for DNA of periodontal pathogens when species-specific primers for detection of periodontal pathogens were used.[160] Similarly, Cairo et al[161] could not demonstrate periodontal bacteria in carotid plaque in a case-control study involving 52 subjects (26 dentate patients in the case group; the control group included 26 edentulous patients)

scheduled for carotid endarterectomy. A small study of 22 patients with periodontitis undergoing coronary artery bypass graft surgery found that periodontal samples from the group with severe periodontitis had a higher prevalence and biomass of bacterial species than did the moderate periodontitis group; however, in combined vessel samples, this prevalence was statistically significant for only 8 of 20 bacterial species. Interestingly, healthy internal mammary artery and saphenous vein specimens had a higher prevalence of periodontal bacteria than did atheromatous plaque specimens in patients with severe periodontitis, which argues against a causal role of direct periodontal pathogen invasion.[162]

Beyond the current interest in PD, the role of infection in the evolution of ASVD has been the subject of extensive investigation (Table 3). Several infective agents have been proposed, including cytomegalovirus, *Helicobacter pylori*, and particularly *Chlamydophila pneumonia,* which has been the most heavily studied. These studies have included in vitro and animal infection models, human seroepidemiological investigations, and clinical trials of antichlamydial antibiotics to prevent ACS.[163,164] *C pneumoniae* or its DNA have been demonstrated in human atheromatous plaques, prompting the hypothesis that this agent might initiate or promote the development of these vascular lesions.[165]

Recovery of viable microorganisms in cultures of human atheroma has been difficult,[122,158] and results of seroepidemiological, polymerase chain reaction, immunohistochemical, and in situ hybridization investigations have been criticized for methodological problems.[122] It has been hypothesized that identified pathogens may be innocent bystanders or that total pathogen burden may be a more relevant marker of risk than evidence of individual microbial infections alone.[166]

Numerous studies have examined the effect of antichlamydial antibiotic therapy on outcomes in patients with coronary artery disease. Of note, systemic antibiotics alone would not be expected to lead to a long-term resolution of chronic periodontitis, in which bacteria reside in a biofilm. In patients with hemodynamically significant coronary artery disease, the AZACS (AZithromycin in Acute Coronary Syndrome), WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders), and ACADEMIC (Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infarction with Chlamydia) studies did not demonstrate cardiovascular benefit at 6, 14, and 24 months' follow-up, respectively, after treatment with azithromycin.[167–169] Several other antibiotic studies also did not demonstrate a significant reduction in primary cardiovascular or mortality end points, including patients with recent ACS.[163,164,170,171] One study found that antibiotic use was associated with reduced cardiovascular events but did not improve mortality.[172] A recently published systematic review and meta-analysis focused on clinical trials that were prospective, randomized, and placebo controlled.[173] Eleven trials that involved >19 000 patients were included in the meta-analysis. Antibiotic regimens were highly variable and included short, intermittent, and prolonged periods of administration that included macrolides, azalides, and a fluoroquinolone. For the defined end points of all-cause mortality, MI, and combined MI and unstable angina, there was no demonstrable benefit of antibiotic therapy.[173] A systematic review by Voils et al[174] did not find sufficient evidence for a role for antibiotics in secondary prevention of adverse cardiovascular events or death in symptomatic coronary heart disease (CHD).

Several randomized, placebo-controlled trials to date have examined the impact of anti-*Chlamydophila* antibiotic therapy in patients with peripheral artery disease.[175–178] Four studies enrolled ≈1300 patients; 3 of the 4 studies demonstrated no benefit in peripheral artery disease–related outcomes among antibiotic recipients. In the absence of evidence supporting improved outcomes, there has been no recommendation from professional societies for antibiotic therapy in the absence of sepsis for patients with MI, unstable angina, peripheral artery disease, or asymptomatic coronary artery disease.

Evidence for an Association Between PD and Cardiovascular Disease

Observational Studies With Clinical Outcomes

Tables 4 through 6 summarize data from epidemiological studies that report odds ratios, hazard ratios, or relative risk estimates and use PD as an exposure for ASVD-related outcomes. Specifically, Table 4 summarizes studies that focused on ASVD. Table 5 includes studies that evaluated evidence related to acute MI or ACS, and Table 6 lists studies related to stroke or cerebral vascular accident. In these studies, PDs as exposure variables have been broadly defined by a variety of measures that include self-reported assessments of tooth loss or periodontal status; clinically or radiographically assessed gingival inflammation and extent and severity of pathological periodontal pockets or clinical attachment loss; bacterial colonization by specific periodontal species; and serum IgG and IgA antibody titers to periodontal pathogens or specific bacterial antigens.

Table 4 includes data from a total of 42 studies. Of these, 26 used clinical or radiographic assessments, and 8 self-reported data on dental or periodontal status; 5 studies analyzed exclusively data on tooth loss and 7 self-reported data on tooth loss; 5 used serological assessments of antibody titers to periodontal microbiota, and 1 study described bacterial colonization patterns. Among the 26 studies that used clinical or radiographic measures of PD, 18 reported a positive association between poor periodontal status and increased odds ratio, hazard ratio, or relative risk for ASVD-related outcomes in adjusted analyses, and another 2 studies reported positive associations in unadjusted analyses. Six studies reported no associations between PD and ASVD-related outcomes after use of multivariate models. Among the studies that analyzed tooth loss data, 10 reported a positive, statistically significant association between advanced tooth loss or edentulism and poor ASVD-related outcomes; 1 study reported a similar association in women only, whereas another found an association for ASVD only and not for CHD; and 2 studies reported no association. Among the studies that used serological assessments, 3 reported positive associations between specific elevated titers and ASVD events, whereas 2 reported no associations. Finally, the single study that used bacterial colonization patterns as a measure of exposure reported a positive association between pathogen burden and ASVD outcomes.

A total of 15 studies that examined the association between PD and MI, ACS, or obstructive disease in ACS patients are summarized in Table 5. The exposure variable was clinical or radiographic assessments of periodontal status in 8 studies,

Table 4. Summary of Epidemiologic Observational Studies on the Association Between Periodontal Diseases and CHD/CAD/ASVD That Reported Estimates for Odds Ratios, Hazard Ratios, or Relative Risk

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Senba et al, 2008[179]	29 909	Japan	<66	Cross-sectional	Self-reported periodontitis or tooth loss	CHD	1–3, 5, 6, 8, 9	OR in males for periodontitis: 1.51 (0.90–2.52); for tooth loss of ≥5 teeth: 1.54 (0.90–2.62); OR in females for periodontitis: 1.48 (0.95–2.32); for tooth loss of ≥5 teeth: 1.68 (1.08–2.61)
Ylostalo et al, 2006[180]	8690	Finland	NR	Cross-sectional	Self-reported gingivitis and tooth loss	Angina pectoris	3, 4	OR for gingivitis: 1.52 (1.04–2.22); OR for tooth loss: 1.53 (0.69–3.42)
Beck et al, 2005[22]	5002	United States (subset of the ARIC study)	45–64	Cross-sectional	Periodontitis (clinical); serum IgG to 17 species	CHD	1–9	OR for high vs low IgG in ever-smokers: *Td* 1.7 (1.2–2.3) *Pi* 1.5 (1.1–2.0) *Co* 1.5 (1.1–2.1) *Vp* 1.7 (1.2–2.3); OR for high vs low IgG in never-smokers: *Pn* 1.7 (1.1.–2.6) *Aa* 1.7 (1.2–2.7) *Co* 2.0 (1.3–3.0) No association with clinical periodontal status
Elter et al, 2004[181]	8363	United States (ARIC)	52–75	Cross-sectional	Periodontitis (clinical); Tooth loss	CHD	5–9, 21	OR for combined high attachment loss and tooth loss:1.5 (1.1–2.0); OR for edentulism: 1.8 (1.4–2.4)
Pussinen et al, 2003[19]	1163 Men	Finland	45–74	Cross-sectional	Serum IgG to *Aa* and *Pg*	CHD	1, 3–5, 7–9	OR for high combined titer: 1.5 (0.95–2.5)
Lowe et al, 2003[182]	1958	Scotland	25–74	Cross-sectional	Self-reported edentulism	ASVD	1, 3–5	OR 1.55 (1.13–2.13)
Persson et al, 2002[183]	1084	United States	60–75	Cross-sectional	Periodontitis (radiographic)	Carotid calcification	Unadjusted	OR for bone loss: 2.1 (1.3–3.2)
Buhlin et al, 2002[184]	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	ASVD	Unadjusted	OR for bleeding gums: 1.60 (1.19–2.15); OR for loose teeth: 0.96 (0.62–1.48); OR for deep pockets: 1.08 (0.78–1.51); OR for dentures: 1.57 (1.13–2.20)
Starkhammar Johansson et al, 2008[185]	323	Sweden	40–75	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 5	OR 5.74 (2.07–15.90)
Amabile et al, 2008[186]	131	France	NR	Case-control	Periodontitis (clinical)	CAD	1, 3–9	OR 2.38 (1.43–3.98)
Colhoun et al, 2008[76]	400	England	30–55	Case-control (type 1 diabetes mellitus)	Serum IgG (*Pg, Aa*)	CA calcification	1–9	OR for those having both titers above the median: 1.4 (0.8–2.6)
Nonnenmacher et al, 2007[18]	90	Germany	40–80	Case-control	Periodontitis (clinical)	CHD	1–3, 5, 9	OR 3.2 (1.2–9.0)
Briggs et al, 2006[187]	171	Ireland	≥40	Case-control	Periodontitis (clinical)	CHD	1–6, 10	OR 3.06 (1.02–9.17)
Spahr et al, 2006[16]	789	Germany	43–73	Case-control	Periodontitis (clinical); colonization by five species (*Aa, Pg, Tf, Pi, Td*)	CHD	1, 3–6, 9, 10	OR for incremental increase in clinical periodontal score by 1 unit: 1.67 (1.08–2.58) OR for incremental increase in "total pathogen burden" by 1 log unit: 1.83 (1.23–2.71)
Geismar et al, 2006[188]	250	Denmark	NR	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 3, 5, 7, 9–11	OR for severe bone loss: 6.6 (1.69–25.6) in ages <60 y
Buhlin et al, 2005[189]	193 Women	Sweden	43–79	Case-control	Periodontitis (clinical/radiographic)	CHD	1, 4–6, 9	OR for high No. of deep pockets: 3.68 (1.68–8.74)
Janket et al, 2004[190]	506	Finland	NR	Case-control	Periodontitis (clinical; asymptotic dental score, ADS)	CHD	7, 14, 15	OR 1.71 (1.36–2.14)
Geerts et al, 2004[191]	170	Belgium	NR	Case-control	Periodontitis (clinical)	CAD	1, 3, 5–8, 10, 11, 16	OR 6.5 (1.8–23)

(*Continued*)

Table 4. Continued

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Dorn et al, 2010[81]	884	United States	35–69	Cohort	Periodontitis (clinical)	Overall ASVD events (fatal, nonfatal, revascularization)	1, 3–5, 7, 9, 11, 16, 18, 25	HR for mean attachment level in never-smokers: 1.43 (1.06–1.91); in ever-smokers: 0.99 (0.86–1.15)
de Oliveira et al, 2010[192]	11 869	Scotland	>35	Cohort	Self-reported oral hygiene	ASVD	1, 3–6, 8, 9, 11, 20, 26	HR for tooth brushing less than once vs at least twice daily: 1.7 (1.3–2.3)
Holmlund et al, 2010[193]	7674	Sweden	20–89	Cohort	Tooth loss; periodontitis (clinical)	CHD and ASVD mortality	1, 3, 5	ASVD mortality: HR for <10 teeth vs >25 teeth: 4.41 (2.47–7.85); HR for severe periodontal disease vs no disease: 1.62 (0.59–4.46). CHD mortality: HR for <10 teeth vs >25 teeth: 7.33 (4.11–13.07); HR for severe periodontal disease vs no disease: 0.78 (0.27–2.21)
Meurman et al, 2003[194]	506	Finland	NR	Case-control	Periodontitis (clinical/radiographic; modified dental index)	CHD	1, 3, 4	OR 1.31 (1.16–1.48)
Dietrich et al, 2008[195]	1203	United States (Normative Aging Study)	21–84	Cohort	Periodontitis (clinical/radiographic)	CHD	1–10	HR for ages <60 y: Clinical, 1.94 (1.23–3.05); radiographic, 2.12 (1.26–3.60). HR for ages ≥60 y: Clinical, 0.73 (0.45–1.19); radiographic: 1.81 (NR)
Heitmann and Gamborg, 2008[196]	2932	Denmark (MONICA)	30–60	Cohort	Tooth loss	Fatal/nonfatal ASVD, CHD	1, 2, 4–6, 8–10	HR (5th vs 1st quintile) for ASVD: 1.50 (1.02–2.19); HR for CHD: 1.31 (0.74–2.31)
Pussinen et al, 2007[197]	505	Finland (FINRISK subset)	25–64	Prospective case-cohort	Serum IgG and IgA to *Aa* and *Pg*	ASVD	1, 3–9	HR for combined high titers: 1.87 (1.13–3.08)
Tu et al, 2007[198]	12 223	Scotland	≤39	Cohort	Tooth loss	ASVD mortality	1, 3–5, 8, 9	HR for those having >9 missing teeth: 1.35 (1.03–1.77)
Pussinen et al, 2005[24]	1023 Men	Finland (Kuopio Ischemic Heart Disease study)	46–64	Cohort	Serum IgA and IgG to *Aa, Pg*	CHD	1, 4–8, 15	RR for high *Aa* IgA: 2.0 (1.2–3.3); RR for high *Pg* IgA: 2.1 (1.3–3.4)
Saremi et al, 2005[199]	628 With type 2 diabetes mellitus	United States (Pima Indians)	≥35	Prospective cohort	Periodontitis (clinical/radiographic)	ASVD mortality	1, 3, 5–7, 9, 13	HR for severe periodontitis: 3.2 (1.1–9.3)
Holm-Pedersen et al, 2005[200]	125	Sweden	≥80	Cohort	Periodontitis (clinical)	Arrhythmia	Unadjusted	OR 1.3 (0.5–3.5)
Hung et al, 2004[201]	100 381	United States HPFS and NHS	40–75	Cohort	Self-reported tooth loss	CHD	1, 5–11, 16	RR for severe tooth loss in men: 1.36 (1.11–1.67); in women: 1.64 (1.31–2.05)
Ajwani et al, 2003[202]	364	Finland	75–85	Cohort	Periodontitis (clinical)	ASVD mortality	1, 3–5, 7–9	RR 1.97 (1.01–3.85)
Tuominen et al, 2003[74]	6527	Finland	30–69	Cohort	Periodontitis (clinical); tooth loss	ASVD mortality	1, 4–8	RR for tooth loss in men: 0.9 (0.5–1.6) in women: 0.3 (0.1–1.0) RR for periodontitis in men: 1.0 (0.6–1.6) in women: 1.5 (0.6–3.8)
Ajwani et al, 2003[203]	364	Finland	76–86	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 4, 7–9, 19	OR for periodontitis: 1.86 (0.96–3.58); OR for edentulism: 1.90 (1.06–3.39)
Hujoel et al, 2002[204]	371	United States (subset of NHANES I with history of ASVD and who were dentate)	NR	Cohort	Periodontitis (clinical)	Incident CHD; fatal CHD	1–12	HR for ASVD and periodontitis: 0.79 (0.54–1.14); HR for ASVD and gingivitis: 0.76 (0.50–1.15); HR for fatal ASVD and periodontitis: 0.75 (0.34–1.66); OR for fatal ASVD and gingivitis: 1.22 (0.57–2.62)
Abnet et al, 2001[205]	29 584	China	40–69	Cohort	Tooth loss	ASVD mortality	1, 3, 5	RR 1.28 (1.17–1.40)
Jansson et al, 2001[206]	1393	Sweden	18–66	Cohort	Periodontitis (clinical/radiographic)	ASVD mortality	1, 3, 5, 19	Incidence OR for periodontitis in ages <45 y: 2.7 (P=0.04)
Howell et al, 2001[207]	22 071	United States (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	ASVD mortality	1, 5, 6, 8–11, 19	RR 1.00 (0.79–1.26)
Hujoel et al, 2000[72]	8032 (NHANES I follow-up study)	United States	25–74	Cohort	Periodontitis (clinical)	CHD events (mortality, hospitalization, revascularization procedure)	1–12	HR for gingivitis: 1.05 (0.88–1.26); HR for periodontitis: 1.14 (0.96–1.36)

(*Continued*)

Table 4. Continued

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Morrison et al, 1999[208]	10 368	Canada	35–84	Cohort	Periodontitis (clinical)	CHD mortality	1, 3, 5–8	RR for severe gingivitis: 2.15 (1.25–3.2); RR for periodontitis: 1.37 (0.80–2.35); RR for edentulism: 1.90 (1.17–3.10)
Joshipura et al, 1996[209]	44 119 men (Health Professionals' Follow-Up Study)	United States	40–75	Cohort	Self-reported oral health status	Incident CHD	1, 5, 9–11, 20, 21	RR in those with periodontitis: 1.04 (0.86–1.25); RR among those reporting periodontitis and ≤10 teeth: 1.67 (1.03–2.71)
Beck et al, 1996[210]	1147 Men	United States	21–80	Cohort	Periodontitis (clinical/radiographic)	Incident CHD	1, 7–9	Incidence OR for those with "high" bone loss: 1.5 (1.04–2.14); incidence OR for those with pockets >3 mm at all their teeth: 3.1 (1.30–7.30)
DeStefano et al, 1993[77]	9760 (NHANES I follow-up study)	United States	25–74	Cohort	Periodontitis (clinical)	Incident fatal and nonfatal CHD	1–11	RR for gingivitis: 1.05 (0.88–1.26); RR for periodontitis: 1.25 (1.06–1.48); RR for edentulism: 1.23 (1.05–1.44)

Studies are grouped according to design (cross-sectional, case-control, or cohort) and sorted by year of publication.

CHD indicates coronary heart disease; CAD, coronary artery disease; ASVD, atherosclerotic vascular disease; OR, odds ratio; NR, not recorded; ARIC, Atherosclerosis Risk In Communities; *Td*, *Treponema denticola*; *Pi*, *Prevotella intermedia*; *Co*, *Capnocytophaga ochracea*; *Vp*, *Veillonella parvula*; *Pn*, *Prevotella nigrescens*; *Aa*, *Aggregatibacter actinomycetemcomitans*; *Pg*, *Porphyromonas gingivalis*; CA, coronary artery; *Tf*, *Tannerella forsythia*; ADS, asymptotic dental score; HR, hazard ratio; MONICA, Monitoring Trends and Determinants in Cardiovascular Disease; FINRISK, Finland Cardiovascular Risk Study; RR, relative risk; HPFS, Health Professionals Follow-Up Study; NHS, National Health Service; and NHANES I, National Health and Nutrition Examination Survey I.

*For cohort studies, the reported age range applies to the baseline examination.

†Describes how periodontitis/oral health status was assessed (clinically, radiographically, by self-reported information, by serological assessment of titers to specific periodontal bacteria, or by assessment of oral microbial colonization).

‡Adjustments: Numbers describe the following variables: (1) Age; (2) race or ethnicity; (3) sex; (4) socioeconomic status (income and/or education); (5) smoking habits; (6) diabetes (presence or duration/hemoglobin A1c); (7) hyperlipidemia (or low-density lipoprotein cholesterol and/or high-density lipoprotein cholesterol and/or triglycerides); (8) hypertension (or systolic and/or diastolic blood pressure); (9) body mass index or waist/hip ratio or obesity; (10) alcohol consumption; (11) physical activity; (12) marital status; (13) microalbuminuria; (14) C-reactive protein; (15) fibrinogen; (16) diet; (17) vitamin E intake; (18) statin intake; (19) history of ASVD; (20) family history of ASVD; (21) current access to dentist; (22) renal disease; (23) papillary bleeding score; (24) dependent living; (25) hypertension medication; (26) frequency of dental visits; (27) oral hygiene; (28) missing teeth; (29) DMFT index (decayed, missing, filled teeth); (30) family history of diabetes; and (31) family history of hypertension.

self-reported periodontitis in 2 studies, tooth loss as the sole exposure in 1 study, levels of systemic antibodies to periodontal pathogens in 2 studies, colonization levels by 6 periodontal species in 1 study, and benzoyl-DL-arginine naphthylamide (BANA), which reflects colonization by 3 gram-negative anaerobic bacteria associated with periodontitis (*P gingivalis, T denticola*, and *T forsythia*), in 1 study. Poor periodontal status was positively associated with higher risk for MI-associated events in all 8 studies that assessed it by means of a clinical periodontal examination. In contrast, 2 studies that used self-reported information on oral status[184,207] found no association between poor periodontal status and MI. Tooth loss was not associated with MI-related events in any of the 3 studies that presented such analyses. The study that used periodontal microbial colonization as the exposure marker found a positive association between high colonization by 2 periodontal pathogens and MI. Use of BANA as a surrogate marker for bacterial colonization in another study suggested a positive association between BANA values and risk for ACS. Two serological studies revealed positive associations between high specific titers and MI-related events, the first for any of the 4 IgG titers tested,[26] whereas the second one[20] found a positive association only for IgA against *P gingivalis*.

Lastly, Table 6 summarizes findings from 22 studies that examined stroke as the dependent variable. With respect to exposure, 5 studies used tooth loss data exclusively, 11 included clinical or radiographic assessments of periodontal status, 4 used self-reported information on oral/periodontal health, and 3 examined antibody responses to periodontal bacteria. Six studies that used tooth loss data reported a positive association between tooth loss and edentulism and stroke, but another 6 failed to document a statistically significant association. In contrast, 11 studies reported positive associations between poor periodontal status and stroke, whereas only 3 studies did not. Among the serological studies, 1 showed no association between high titers and stroke,[80] 1 showed a statistically significant inverse association between high serum antibodies to *A actinomycetemcomitans* leukotoxin and stroke in women only,[226] and 1 showed a statistically marginal association between high serum IgA to *A actinomycetemcomitans* and *P gingivalis* that was differentially based on ASVD history.[21]

Observational Studies Using Noninvasive Imaging Correlates or Surrogate Markers of ASVD

Many imaging tools and surrogate markers for atherosclerosis are in clinical and experimental use. Some identify anatomic changes at subclinical stages, whereas others reflect functional aberrations in the vasculature or end-organ impact. A systematic review on the use of a broad spectrum of such methods in subjects with PD included screening computed tomography of the coronary arteries, ultrasound of the carotid arteries, magnetic resonance imaging, ankle-brachial index, microalbuminuria and other biochemical measures of kidney dysfunction, flow-mediated vasodilation (FMD) of the brachial artery (as a marker of endothelial function), and pulse waveform analysis. The authors found that these measures are not highly

Table 5. Summary of Epidemiological Observational Studies on the Association Between Periodontal Diseases and Myocardial Infarction or Acute Coronary Syndrome That Reported Odds Ratios, Hazard Ratios, or Relative Risk

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Gotsman et al, 2007[211]	201	Israel	NR	Cross-sectional	Periodontitis (clinical)	ACS	1, 5, 7, 8	OR for % of teeth with CAL ≥5 mm: 1.03 (1.01–1.04)
Accarini and de Godoy, 2006[212]	361	Brazil	27–89	Cross-sectional	Periodontitis (clinical)	Obstructive disease in ACS patients	Unadjusted	OR 2.57 (1.19–5.54)
Holmlund et al, 2006[213]	4254	Sweden	20–70	Cross-sectional	Periodontitis (clinical/radiographic)	Self-reported, hospital-treated MI	1, 3, 5	OR for bone loss in ages 40–60 only: 2.69 (1.12–6.46)
Buhlin et al, 2002[184]	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Self-reported MI	Unadjusted	OR for bleeding gums: 0.55 (0.22–1.36); OR for loose teeth: 0.98 (0.32–3.04); OR for deep pockets: 1.32 (0.51–3.38); OR for dentures: 1.04 (0.47–2.30)
Arbes et al, 1999[214]	5564 (NHANES III)	United States	40–90	Cross-sectional	Periodontitis (clinical)	Self-reported heart attack	1–9	OR for highest vs lowest extent of attachment loss: 3.77 (1.46–9.74)
Adriankaja et al, 2011[215]	1060	United States	35–69	Case-control	Presence of 6 periodontal pathogens (*Pg, Tf, Pi, Cr, Fn, Es*)	MI	1, 3–8	OR for *Tf*: 1.62 (1.18–1.22); *Pi*: 1.4 (1.02–1.92)
Lund Håheim et al, 2008[26]	1173 men	Norway	48–77	Case-control	Serum IgG to *Pg*, *Aa*, *Td*, and *Tf*	Self-reported MI	5–9, 14	OR for seropositivity for any of the 4 titers: 1.30 (1.01–1.68)
Rech et al, 2007[216]	114	Brazil	NR	Case-control	Periodontitis (clinical)	ACS	1, 3, 5, 6	OR 4.5 (1.3–15.6)
Rubenfire et al, 2007[217]	440	United States	NR	Case-control	Positive BANA test	ACS	1, 3, 5, 22, 23	OR in BANA-positive participants: 3.95 (1.61–9.71)
Andriankaja et al, 2007[218]	1461	United States	35–69	Case-control	Periodontitis (clinical)	Nonfatal MI	1, 3, 5–8	OR for mean attachment loss: 1.46 (1.26–1.69)
Cueto et al, 2005[219]	149	Spain	40–75	Case-control	Periodontitis (clinical; partial recording)	MI	1, 3, 5–7, 11	OR for extensive periodontitis: 3.31 (1.42–7.71)
Pussinen et al, 2004[20]	126	Finland	30–59	Case-control	Serum IgA and IgG to *Pg* and *Aa*	Nonfatal and fatal MI	5–9	OR for 4th vs 1st quartile of titer level; OR for *Aa* IgA: 0.60 (0.20–1.83); OR for *Aa* IgG: 0.42 (0.14–1.31); OR for *Pg* IgA: 3.99 (1.22–13.10); OR for *Pg* IgG: 0.54 (0.18–1.60)
Lopez et al, 2002[220]	61	Chile	30–50	Case-control	Periodontitis (clinical)	Hospitalization because of MI, unstable angina, or angina pectoris	5, 6, 8	OR for mean attachment level: 3.17 (1.31–7.65); OR for mean probing depth: 8.64 (1.22–61.20); OR for mean No. of teeth: 0.93 (0.83–1.04)
Syrjala et al, 2009[221]	392 Never-smokers	Finland	≥75	Cohort	Tooth loss	MI	1, 3, 4, 6–11	Prevalence proportion ratio for No. of teeth (continuous): 1.01 (0.97–1.05); Prevalence proportion ratio for dentate vs edentulous: 0.9 (0.5–1.8)
Howell et al, 2001[207]	22 071	United States (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	Nonfatal MI	1, 5, 6, 8–11, 19	RR 1.01 (0.82–1.24)

Studies are grouped according to design (cross-sectional, case-control, or cohort) and sorted by year of publication.

NR indicates not recorded; ACS, acute coronary syndrome; OR, odds ratio; CAL, clinical attachment level; MI, myocardial infarction; NHANES III, National Health and Nutrition Examination Survey III; *Pg*, *Porphyromonas gingivalis*; *Tf*, *Tannerella forsythia*; *Pi*, *Prevotella intermedia*; *Cr*, *Campylobacter rectus*; *Fn*, *Fusobacterium nucleatum*; *Es*, *Eubacterium saburreum*; *Aa*, *Aggregatibacter actinomycetemcomitans*; *Td*, *Treponema denticola*; BANA, benzoyl-DL-arginine naphthylamide; and RR, relative risk.

*For cohort studies, the reported age range applies to the baseline examination.

†Describes how periodontitis/oral health status was assessed (clinically, radiographically, by self-reported information, by serological assessment of titers to specific periodontal bacteria, or by assessment of oral microbial colonization).

‡Adjustments: Numbers describe the following variables: (1) Age; (2) race or ethnicity; (3) sex; (4) socioeconomic status (income and/or education); (5) smoking habits; (6) diabetes (presence or duration/hemoglobin A1c); (7) hyperlipidemia (or low-density lipoprotein cholesterol and/or high-density lipoprotein cholesterol and/or triglycerides); (8) hypertension (or systolic and/or diastolic blood pressure); (9) body mass index or waist/hip ratio or obesity; (10) alcohol consumption; (11) physical activity; (12) marital status; (13) microalbuminuria; (14) C-reactive protein; (15) fibrinogen; (16) diet; (17) vitamin E intake; (18) statin intake; (19) history of ASVD; (20) family history of ASVD; (21) current access to dentist; (22) renal disease; (23) papillary bleeding score; (24) dependent living; (25) hypertension medication; (26) frequency of dental visits; (27) oral hygiene; (28) missing teeth; (29) DMFT index (decayed, missing, filled teeth); (30) family history of diabetes; and (31) family history of hypertension.

correlated with each other and do not fully substitute for studies of clinical ASVD end points.[235] Nevertheless, these methods have proved useful in clinical investigations of specific ASVD manifestations in defined patient cohorts and have been applied to the question of a possible PD/ASVD link.

Association of Periodontitis With Subclinical Carotid or Coronary Artery Disease

Detection of ASVD before its clinical presentation is an important goal. Direct visualization of the coronary circulation with computed tomographic methods can reveal calcification of vessels that identifies the atherosclerotic process and may have a role in stratifying patient risk. Atherosclerosis in noncoronary arterial beds such as the carotid arteries or peripheral arteries is correlated with coronary artery involvement, and ultrasound-based measurement of carotid intima-media thickness (cIMT) is considered a surrogate marker of coronary artery disease that has been validated in large population studies such as the Multi-Ethnic Study of Atherosclerosis (MESA).[236]

Table 6. Summary of Epidemiologic Observational Studies on the Association Between Periodontal Diseases and Stroke That Reported Odds Ratios, Hazard Ratios, or Relative Risk

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Lee et al, 2006[222]	5123	United States	60 to ≥76	Cross-sectional	PHS (a composite index of periodontitis and tooth loss)	Self-reported history of stroke	1, 5, 6, 8, 10, 14	OR for PHS class 5 vs class 1: 1.56 (0.95–2.57)
Elter et al, 2003[223]	10 906	United States	NR	Cross-sectional	Periodontitis (clinical); edentulism	Ischemic stroke or TIA	1–9, 21	OR for highest quartile of AL: 1.3 (1.02–1.7); OR for edentulism: 1.4 (1.5–2.0)
Buhlin et al, 2002[184]	1577	Sweden	41–84	Cross-sectional	Self-reported oral status	Stroke§	Unadjusted	OR for bleeding gums: 1.83 (0.78–4.31); OR for loose teeth: 1.83 (0.66–5.12); OR for deep pockets: 0.68 (0.22–2.05); OR for dentures: 1.81 (0.74–4.42)
Kim et al, 2010[224]	379	Korea	40–79	Case-control	Periodontitis (clinical)	Hemorrhagic stroke	1, 3–6, 8–10, 19, 26–31	OR for presence of attachment level ≥6 mm: 2.53 (1.14–5.61)
Pradeep et al, 2010[225]	200	India	33–68	Case-control	Periodontitis (clinical)	Acute cerebral ischemia	1, 3–6, 8, 10, 27	OR for mean pocket depth >4.5 mm: 8.5 (1.1–68.2)
Sim et al, 2008[79]	479	Korea	40–79	Case-control	Periodontitis (clinical)	Stroke§	4–6, 8–10, 19–21	OR for severe periodontitis: 4.30 (2.27–8.16)
Pussinen et al, 2007[80]	893	Finland	45–74	Case-control	Serum IgG and IgA to *Aa* and *Pg*	Stroke§	1, 4, 5, 7–10	OR for seropositivity for *Aa* IgA: 0.83 (0.62–1.1); OR for *Aa IgG:* 0.93 (0.66–1.32); OR for *Pg* IgA: 1.22 (0.91–1.65); OR for *Pg* IgG: 1.31 (0.97–1.76)
Johansson et al, 2005[226]	819	Sweden	25–74	Case-control	Serum antibodies to *Aa* leukotoxin	Stroke§	4–9	OR for seropositivity in men: 0.88 (0.52–1.51); OR for seropositivity in women: 0.28 (0.13–0.59)
Dorfer et al, 2004[227]	603	Germany	18–25	Case-control	Periodontitis, gingivitis (clinical/radiographic)	Ischemic stroke	1, 3–6, 8, 19	OR for severe gingivitis: 18.29 (5.84–57.26); OR for CAL >6 mm: 7.38 (1.55–15.03); OR for severe bone loss: 3.62 (1.58–8.28)
Pussinen et al, 2004[21]	500	Finland	45–64	Case-control	Serum IgG and IgA to *Pg* and *Aa*	Stroke	1, 3, 5–10	OR for IgA seropositivity to *Aa* in participants free of ASVD at baseline: 1.6 (1.0–2.6); OR for IgA seropositivity to *Pg* in participants with ASVD at baseline: 2.6 (1.0–7.0)
Grau et al, 2004[228]	771	Germany	18–75	Case-control	Periodontitis (clinical)	Ischemic stroke or TIA	1, 3–6, 8, 10, 19	OR for clinical attachment loss >6 mm: 4.34 (1.85–10.2)
Loesche et al, 1998[229]	401	United States	≥60	Case-control	Periodontitis (clinical)	CVA	1–3, 5–7, 9, 24	OR for % teeth with AL>6 mm: 1.04 (1.01–1.07); OR for % of teeth with PD >6 mm: 0.96 (0.92–1.01); OR for 15–28 teeth present vs 1–14 teeth present: 3.29 (1.33–8.16)
Holmlund et al, 2010[193]	7674	Sweden	20–89	Cohort	Tooth loss; periodontitis (clinical)	Stroke mortality	1, 3, 5	HR for <10 teeth vs >25 teeth: 0.91 (0.24–3.49); HR for severe periodontal disease vs no disease: 1.39 (0.18–10.45)
Choe et al, 2009[230]	867 256	Korea	30–95	Cohort	Tooth loss	Stroke§	1, 5–11	HR for men having ≥7 missing teeth: 1.3 (1.2, 1.4); HR for women having ≥7 missing teeth: 1.2 (1.0, 1.3)
You et al, 2009[231]	2862	United States	45 to ≥85	Cohort	Self-reported tooth loss	Self-reported stroke	1–8, 14, 19	OR for participants having ≥17 missing teeth: 1.27 (1.09, 1.49)
Syrjala et al, 2009[221]	392 Never-smokers	Finland	≥75	Cohort	Tooth loss	Stroke§	1, 3, 4, 6–11	Prevalence proportion ratio for No. of teeth (continuous): 1.02 (0.94–1.08); Prevalence proportion ratio for dentate vs edentulous: 0.9 (0.2–2.8)
Tu et al, 2007[198]	12 223	Scotland	≤39	Cohort	Tooth loss	Stroke§	1, 3–5, 8, 9	HR for those having >9 missing teeth: 1.64 (0.96–2.80)
Abnet et al, 2005[232]	29 584	China	40–69	Cohort	Tooth loss	Fatal stroke	1, 3, 5, 8, 9	RR for those with less than the median age-specific No. of teeth: 1.11 (1.01–1.23)
Joshipura et al, 2003[233]	41 380 Men	United States	40–75	Cohort	Self-reported periodontitis/tooth loss	Ischemic stroke	1, 4–11, 17	HR for those with ≤24 teeth: 1.57 (1.24–1.98); HR for those with periodontitis: 1.33 (1.03–1.70)
Wu et al, 2000[234]	9962	United States	25–74	Cohort	Gingivitis, periodontitis (clinical); edentulism	Ischemic stroke	1–10	RR for gingivitis: 1.24 (0.74–2.08); RR for periodontitis: 2.11 (1.30–3.42); RR for edentulism: 1.41 (0.96–2.06)

(*Continued*)

Table 6. Continued

Study	N	Country	Age Range, y*	Design	Exposure†	Outcome	Adjustments‡	Measure of Association
Howell et al, 2001[207]	22 071	United States (Physicians Health Study)	40–84	Cohort	Self-reported periodontitis	Nonfatal stroke	1, 5, 6, 8–11, 19	RR 1.10 (0.88–1.37)
Morrison et al, 1999[208]	10 368	Canada	35–84	Cohort	Gingivitis, periodontitis (clinical)	Stroke mortality	1, 3, 5–8	RR for severe gingivitis: 1.81 (0.77–4.25) RR for periodontitis: 1.63 (0.72–3.67) RR for edentulism: 1.63 (0.77–3.42)

Studies are grouped according to design (cross-sectional, case-control, or cohort) and sorted by year of publication.

PHS, periodontal health status, a composite index of periodontitis and tooth loss; OR, odds ratio; NR, not recorded; TIA, transient ischemic attack; AL, attachment level ≥3 mm; *Aa*, *Aggregatibacter actinomycetemcomitans*; *Pg*, *Porphyromonas gingivalis*; CAL, clinical attachment level; ASVD, atherosclerotic vascular disease; CVA, cerebral vascular accident; PD, pocket depth; HR, hazard ratio; and RR, relative risk.

*For cohort studies, the reported age range applies to the baseline examination.

†Describes how periodontitis/oral health status was assessed (clinically, radiographically, by self-reported information, by serological assessment of titers to specific periodontal bacteria, or by assessment of oral microbial colonization).

‡Adjustments: Numbers describe the following variables: (1) Age; (2) race or ethnicity; (3) sex; (4) socioeconomic status (income and/or education); (5) smoking habits; (6) diabetes (presence or duration/hemoglobin A1c); (7) hyperlipidemia (or low-density lipoprotein cholesterol and/or high-density lipoprotein cholesterol and/or triglycerides); (8) hypertension (or systolic and/or diastolic blood pressure); (9) body mass index or waist/hip ratio or obesity; (10) alcohol consumption; (11) physical activity; (12) marital status; (13) microalbuminuria; (14) C-reactive protein; (15) fibrinogen; (16) diet; (17) vitamin E intake; (18) statin intake; (19) history of ASVD; (20) family history of ASVD; (21) current access to dentist; (22) renal disease; (23) papillary bleeding score; (24) dependent living; (25) hypertension medication; (26) frequency of dental visits; (27) oral hygiene; (28) missing teeth; (29) DMFT index (decayed, missing, filled teeth); (30) family history of diabetes; and (31) family history of hypertension.

§Ischemic and hemorrhagic stroke.

Increased cIMT has correlated with PD in several association studies, which demonstrated that severe periodontitis,[237] high subgingival colonization concentrations by specific periodontal pathogens,[15] and high serum IgG titers against individual periodontal bacteria[23] were significantly related to increased cIMT in adjusted analyses. A retrospective case study by Beckstrom et al[238] found a significant direct correlation between periodontal bone loss and carotid artery calcifications on panoramic radiographs. Söder et al[239] concluded in a case-control study that cIMT and intima-media area were significantly higher in women with PD than in control subjects. An earlier prospective case-control study by Söder et al[240] also found significantly higher mean values of cIMT and carotid intima-media area in patients with PD compared with control subjects. PD was a principal independent predictor of the common carotid intima-media area (odds ratio, 5.20; $P=0.003$) and cIMT (odds ratio, 4.64; $P=0.004$) in a multiple logistic regression model.[240]

In patients with chronic kidney disease, Franek et al[241] noted significantly higher serum CRP concentration (13.2 ± 11.4 mg/L versus 10.4 ± 14.4 mg/L; $P<0.05$) and cIMT (0.742 ± 0.028 versus 0.656 ± 0.019; $P<0.05$) in patients with advanced periodontitis than in patients without PD. Genctoy et al[242] noted a significant positive correlation between mean cIMT and gingival index in 83 renal transplant recipients with varying degrees of PD even in the absence of systemic inflammation and after adjusting for confounding variables. Desvarieux et al[15] evaluated the relationship between periodontal microbiology and subclinical atherosclerosis in a dentate subset of the Oral Infections and Vascular Disease Epidemiology (INVEST) Study and found that periodontal bacterial burden was related to cIMT across tertiles of bacterial colonization by a subset of a priori defined periodontal pathogens ($P=0.002$), although CRP values were unrelated to periodontal microbial status ($P=0.82$). In a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Study who received a complete periodontal examination, a significant direct relationship between IgG antibody reactive to oral organisms and subclinical atherosclerosis by cIMT ≥1 mm was noted in both ever- and never-smokers.[23]

Detection of coronary artery calcium (CAC) by computed tomography has been promoted as a marker of risk for future ASVD events. The 2007 ACC/AHA expert consensus statement on CAC scoring by computed tomography judged that it may be reasonable to use CAC measurement in asymptomatic patients with intermediate CHD risk (between 10% and 20% 10-year risk of estimated coronary events) on the basis of available evidence that demonstrates incremental risk prediction information in this selected patient group.[243,244] Use of CAC measurements was not recommended for those in other risk categories or with CHD risk equivalents. PD was not considered as a clinical factor in the use of CAC scoring, and no data are available regarding its role in defining ASVD risk in that patient population.

Association of Periodontitis With Endothelial Dysfunction

Vascular endothelium serves a number of vital cardiovascular functions, including regulation of vasomotor tone via nitric oxide and other mediators, prevention of thrombosis, and regulation of interaction between the blood vessel wall and platelets, leukocytes, and monocytes.[245] Endothelial dysfunction may be the earliest vascular manifestation of ASVD and has been associated with traditional risk factors associated with ASVD.[246] It has also been associated with nontraditional risk factors for ASVD, including systemic inflammation, obesity, and physical inactivity, among others.[246] Endothelial dysfunction has been demonstrated among subjects with clinically apparent ASVD, including coronary and peripheral atherosclerosis, preeclampsia, congestive heart failure, pulmonary hypertension, and septic shock.[246] Even among patients free of clinically apparent ASVD, endothelial dysfunction has been associated with an increased risk of incident cardiovascular adverse events during subsequent follow-up.[246–249] Interventions associated with ASVD risk reduction, such as smoking cessation, use of statin therapy, and angiotensin-converting enzyme inhibitors, improve endothelial function in clinical trials.[246] Other interventions that improved endothelial function in physiological research studies (eg,

L-arginine, antioxidant vitamins), however, have shown no benefit in clinical end points and have even shown the potential for harm when studied in large-scale, randomized clinical trials.[250,251]

A number of tools are used to assess endothelial function in vivo.[246,252] Traditional invasive techniques to assess endothelial function required intracoronary or other intra-arterial injections of vasoactive substances such as acetylcholine. More recently, noninvasive methods such as high-resolution ultrasound assessment of the brachial artery after FMD or nitroglycerin administration and digital pulse amplitude tonometry have been studied across a broad spectrum of patient populations.[253] Important limitations of these methods have been described, and their reliable use requires careful attention to calibration, interobserver variability, ambient temperature, and hormonal effects in premenopausal women. The degree to which such exacting methodologies have been applied is not well defined in many studies, and their conclusions must be interpreted with acknowledgement of that limitation.

Endothelial function in humans with PD has been studied in a small number of subjects, with variable control of the important patient, operator, and technical limitations described above.[254–256] Amar and colleagues[254] compared endothelial function as assessed by brachial artery FMD among 26 subjects with severe PD graded by use of standardized diagnostic criteria versus 29 control subjects with no evidence of PD. None of the subjects had known ASVD or documented cardiovascular risk factors. FMD was significantly reduced among subjects with PD compared with control subjects (7.8% versus 11.7%; $P=0.005$). There was no significant difference in the endothelium-independent vasodilatory response to sublingual nitroglycerin administration in the 2 groups. CRP levels were significantly higher among subjects with advanced PD than among control subjects. In a subsequent analysis, no significant difference in FMD was found between subjects with mild PD and control subjects, which suggests a dose-response effect to the degree of PD and the degree of endothelial dysfunction.[254] Seinost and colleagues[256] reported similar impairment in brachial artery FMD among otherwise healthy subjects with advanced PD (n=30) compared with control subjects (n=31; 6.1% versus 8.5%, $P=0.002$). Mercanoglu and colleagues[257] reported impairment in both brachial artery FMD and endothelium-independent vasodilatory response to sublingual nitroglycerin in otherwise healthy subjects with periodontitis compared with healthy control subjects. Periodontal therapy was associated with significant improvement in both FMD and nitroglycerin response in this cohort.

Higashi and colleagues[255] used strain-gauge plethysmography for assessment of forearm blood flow in response to intra-arterial infusion of acetylcholine to assess endothelial function in healthy and hypertensive subjects with and without PD. Among 52 male subjects without ASVD or established risk factors, the presence of self-reported and dentist-confirmed PD was associated with a blunted forearm blood flow response to acetylcholine infusion compared with subjects without PD. There was no difference in the endothelium-independent response to sodium nitroprusside. Furthermore, among subjects with PD who were referred to a 24-week treatment program for PD, there was a statistically significant improvement in forearm blood flow response to acetylcholine compared with pretreatment values. Similar experiments were undertaken by these investigators among 38 male and female subjects with hypertension with and without PD.[255] Hypertensive subjects with PD had impaired forearm blood flow response to acetylcholine administration compared with subjects without PD. Among hypertensive patients with PD who underwent a treatment program, endothelial function improved significantly, to levels comparable to reported values for healthy control subjects.

Association of Periodontitis With Systemic Inflammation

Periodontitis is associated with both local and systemic inflammation. Multiple cytokines and inflammatory markers, including IL-1, IL-6, IL-8, and tumor necrosis factor, are abundantly produced locally in the gingiva of patients with periodontitis and can be recovered in gingival crevicular fluid samples obtained from involved tooth sites.[258,259] Although it has been postulated that these locally produced inflammatory mediators are introduced into the blood stream, periodontitis has not been shown to induce a sustained elevation of plasma IL-1β[260] or tumor necrosis factor-α.[261] Nevertheless, chronic periodontal infection contributes to systemic inflammation characterized by elevation of acute phase proteins, including inflammatory cytokines such as IL-6,[92] coagulation factors such as fibrinogen,[95] and CRP.[92–95]

CRP has been linked to incident MI, stroke, peripheral arterial disease, and sudden cardiac death in multiple prospective epidemiological studies,[84] and it predicts risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency departments with ACS. CRP is not the only inflammatory biomarker that has been shown to predict MI and stroke; however, other markers have less clinical utility because the assays required for their assessment are either inappropriate for routine clinical use or the protein of interest has too short a half-life for clinical evaluation.[85] In contrast, CRP is highly stable, allowing accurate measures in both fresh and frozen plasma without requirements for special collection procedures, and high-sensitivity assays have been standardized across many commercial platforms.[85] Thus, CRP is an attractive screening tool for systemic inflammation in patients with PD, although it is not specific for that disorder.

Helfand et al[262] performed a systematic review of risk factors and surrogate markers with the potential to improve global risk assessment for CHD, including CRP, CAC score as measured by electron-beam computed tomography, lipoprotein(a) level, homocysteine level, leukocyte count, fasting blood glucose, PD, ankle-brachial index, and cIMT. Good-quality studies relevant to the prediction of major CHD events using indices of PD, ankle-brachial index, or cIMT were sparse, so that data were insufficient for estimating pooled risk ratios for major CHD events. PD was deemed an independent, although relatively weak, risk factor for CHD. The authors did not find any direct evidence that periodontal examination would be useful for reclassifying people identified as at intermediate risk by the Framingham risk score. CRP was the best candidate for use in screening and the most rigorously studied, but evidence that changes in CRP level lead to primary prevention of CHD events was inconclusive.[262] In another study, Willershausen et al[263] found that patients with acute MI exhibited an unfavorable dental state of health after statistical adjustment for age, sex, and smoking. That study did not find a significant correlation between CRP and the number of dental apical lesions on radiography.[263]

Association of Periodontitis With ECG Abnormalities

Abnormal ECG findings are often nonspecific and may be associated with atherosclerotic and nonatherosclerotic cardiac diseases, including hypertensive, valvular, and infiltrative disorders. Studies of prevalence of ECG changes in octogenarians, Pima Indians, and a Japanese population have suggested that the risk for ECG abnormalities increases with the severity of PD.[199,264,265] In a different Japanese cohort study, no correlation between PD and prevalence of electrocardiographic abnormalities was found.[266] Thus, the independent correlation of ECG findings with PD has not been definitively proven.

Periodontal Intervention and ASVD Risk

Whether or not treatment of PD modifies the risk for or complications of ASVD has yet to be established. The majority of studies published have examined the effects of different forms of periodontal therapy on markers of systemic inflammation or on surrogate markers of subclinical ASVD.

Periodontal therapy consists of mechanical debridement of root surfaces accompanied by home-based plaque control (tooth brushing and flossing). Mechanical debridement can be performed nonsurgically or in combination with gingival flap elevation (surgical periodontal therapy). Supragingival debridement, which does not constitute full periodontal therapy, has been used as a control treatment in some studies.

Several cohort studies and randomized clinical trials have reported improvements in endothelial function and associated markers of inflammation among subjects with significant PD who have undergone nonsurgical periodontal therapy, with or without systemic antibiotics,[181–183,267,268] which supports the theory that if cardiovascular toxicity from PD occurs, it is mediated at least in part through inflammation and endothelial dysfunction.[181–183,267]

Recently, a randomized controlled trial involving full-mouth mechanical debridement by either surgical or nonsurgical approaches, dictated by the patient's condition, completed within a single session and accompanied by extensive application of local antibiotics in all deep periodontal pockets demonstrated a significant improvement in brachial artery FMD at a 6-month follow-up examination.[261] Notably, this intense intervention resulted in a transient deterioration of FMD and a significant increase in multiple plasma inflammatory mediators immediately after debridement, which supports the notion that bacterial inoculation and other procedure-related inflammation resulting from mechanical debridement has immediate negative effects on endothelial function. In another study based on the US Medicaid claims database, investigators found a transient increased risk for MI and stroke within the first 4 weeks after invasive dental procedures (including periodontal therapy or dental surgery); risk returned to baseline over the subsequent 12 to 24 weeks after treatment.[269]

A review of intervention studies that investigated the effects of periodontal therapy on plasma levels of inflammatory mediators revealed inconsistent findings. Patients treated by nonsurgical periodontal therapy displayed a significant increase in plasma tumor necrosis factor-α, CRP, and IL-6 levels immediately after intervention, which suggests a systemic acute-phase response, possibly caused by massive bacterial inoculation in conjunction with instrumentation of periodontal tissues.[267,270–272] Two smaller studies,[273,274] 1 with surgical and 1 with nonsurgical periodontal therapy followed by a short course of systemic antibiotics, reported no significant changes in serum levels of CRP, IL-6, or tumor necrosis factor-α 3 months after therapy. In contrast, in a 6-month posttreatment follow-up of subjects enrolled in a single-arm intervention study involving nonsurgical periodontal therapy,[275] significant reductions in serum IL-6 (median, decrease 0.2 ng/L; 95% confidence interval, 0.1–0.4 ng/L) and CRP (median decrease, 0.5 mg/L; 95% confidence interval, 0.4–0.7 mg/L) were demonstrated. A subsequent randomized controlled pilot trial by the same investigators compared nonsurgical periodontal therapy alone versus identical therapy supplemented by local adjunctive minocycline application[276] and found statistically significant reductions in serum CRP and IL-6 in both treatment arms, as well as a significant reduction in total and low-density lipoprotein cholesterol in the group that received adjunctive local antibiotic. Yet in a larger randomized controlled trial by the same research group,[267] no significant differences posttreatment were reported in plasma levels of CRP, IL-6, and plasminogen activator inhibitor-1 between the treatment and control groups at 6 months. The treatment group had a reduction in serum soluble E-selectin concentration and neutrophil counts.

The most recent available systematic review of 6 treatment studies investigating the effects of periodontal therapy on serum CRP levels[277] concluded that there is modest evidence of a treatment-induced reduction in CRP (weighted mean difference of reductions of 0.50 mg/L; 95% confidence interval, 0.08–0.93 mg/L). Substantial heterogeneity in short-term responses in inflammatory markers after surgical periodontal therapy has been shown in a single-arm intervention study of 19 biomarkers in patients with moderate to severe periodontitis.[278] In that study, approximately one third of treated patients showed a marked reduction in systemic inflammation, one fourth showed a pronounced increase in systemic inflammation, and the remaining patients had no change. Treatment resulted in discernible changes in the transcriptome gene expression of peripheral blood monocytes, notably in several genes related to innate immunity, apoptosis, and cell signaling, in a manner compatible with the promotion of an antiatherogenic phenotype.[279] A recent pilot study indicated that nonsurgical treatment of mild to moderate periodontitis in otherwise healthy individuals may significantly reduce cIMT at 12 months after completion of treatment.[280]

To date, only a single multicenter pilot study has examined the effects of periodontal therapy on the secondary prevention of cardiac events. The Periodontitis and Vascular Events (PAVE) investigation[281,282] randomized patients with periodontitis and a history of CHD (angiographically proven coronary artery disease or recent MI or surgical or percutaneous coronary revascularization) to either community care (generally consisting of supragingival debridement only; control group) or a study protocol that consisted of oral hygiene instruction and nonsurgical periodontal therapy. Over a 25-month follow-up period, adverse cardiovascular events occurred with similar frequency in the community and the periodontal treatment groups. Periodontal therapy resulted in limited improvement of periodontal status at 6 months after

the intervention, but this was not sustainable at 1-year follow-up. A substantial proportion of individuals randomized to the community care group received some form of preventive or periodontal care outside the study, which complicates interpretation of the study's findings. Lastly, obesity appeared to nullify periodontal treatment effects on a reduction in serum CRP levels. Important lessons were learned by this pilot trial that will likely impact the design of future randomized controlled trials. This includes the requirement for sustained efforts in periodontal intervention to obtain clinically and biologically meaningful positive effects on periodontal status and an appreciation for the role of associated ASVD risk factors that might alter the impact of a treatment-induced improvement in systemic inflammation.

Evidence for PD as a Risk Factor for ASVD

The potential associations between PD and ASVD can be considered in light of published standards for levels of evidence that include Level of Evidence A, for which supportive data are derived from multiple randomized clinical trials or meta-analyses, and Level of Evidence B, for which data derive from a single randomized trial or nonrandomized studies. An association between PD and ASVD is supported by evidence that meets standards for Level of Evidence A. A benefit of periodontal intervention in decreasing local periodontal inflammation is also supported by level A evidence. Causation of ASVD by PD is not supported by either level A or level B evidence. The same is true about a benefit of periodontal intervention in decreasing long-term systemic inflammation.

Summary Assessment of the Literature

The relation between PD and ASVD is potentially of great public health importance because of their high prevalence. Extensive review of the literature indicates that PD is associated with ASVD independent of known confounders. This information comes mostly from observational studies, however, and therefore does not demonstrate that PD is a cause of ASVD, nor does it confirm the contention that therapeutic periodontal interventions prevent heart disease or stroke or modify the clinical course of ASVD. Although a contribution of PD to ASVD is biologically plausible, periodontal and cardiovascular diseases share multiple risk factors that are prevalent and powerful promoters of disease, including tobacco use, diabetes mellitus, and age.

The role of tobacco use in the observed association between PD and ASVD outcomes is a critical one, because smoking is a major risk factor for both conditions, and smoking cessation is a critical component of health maintenance and prevention of many diseases, including both PD and ASVD. Recent evidence indicates that the observed association between PD and ASVD is independent of smoking, because it has been shown retrospectively and longitudinally that PD and ASVD are associated both in smokers and in never-smokers.

Available data indicate a general trend toward a periodontal treatment–induced suppression of systemic inflammation and improvement of noninvasive markers of ASVD and endothelial function. The effects of PD therapy on specific inflammatory markers are not consistent across studies, and their sustainability over time has not been established convincingly, however, and determinants of variability in these responses remain poorly understood. In addition, transient proinflammation and deranged endothelial functions are observed after intensive therapy for PD.

This review highlights significant gaps in our scientific understanding of the interaction of oral health and ASVD. Identification of clinically relevant aspects of their association or therapeutic strategies that might improve the recognition or therapy of ASVD in patients with PD would require further study in well-designed controlled interventional studies. Such investigations should reflect the longitudinal effectiveness of different approaches to managing periodontal health, given the possibility of PD recurrence after therapy and the extended time course of evolution of ASVD and its manifestations. Uniform criteria for PD case definition, extent, and severity; standardized treatment protocols; and consideration of time course, important confounders, and effect modifiers on the association of PD and ASVD would also improve future studies. Finally, the implications of the observed transient detrimental effects of PD therapy on markers of inflammation and endothelial function should be clarified. In the meantime, statements that imply a causative association between PD and specific ASVD events or claim that therapeutic interventions may be useful on the basis of that assumption are unwarranted.

Acknowledgments

The authors wish to thank Donna Stephens for coordinating the literature review and Writing Group functions; Tainika Williams for her word processing and reference manager skills; Anne Olson for her skills as a medical artist; and Bridget Loven for designing and conducting the literature searches.

Appendix

Abbreviations List

ABI	Ankle-brachial index
ACS	Acute coronary syndrome
ASVD	Atherosclerotic vascular disease
BANA	Benzoyl-DL-arginine naphthylamide
CAC	Coronary artery calcium
CHD	Coronary heart disease
cIMT	Carotid intima-media thickness
CRP	C-reactive protein
CVA	Cerebral vascular accident
FMD	Flow-mediated vasodilation
HR	Hazard ratio
HSP	Heat shock protein
IL	Interleukin
MI	Myocardial infarction
OR	Odds ratio
PD	Periodontal disease
RR	Relative Risk

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Peter B. Lockhart	Carolinas Medical Center	None	None	None	None	None	None	None
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Kathryn A. Taubert	World Heart Federation	None	None	None	None	None	None	None
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Walter R. Wilson	Mayo Clinic	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Moise Desvarieux	Columbia University	None	None	None	None	None	None	None
Phillipe Hujoel	University of Washington	None	None	None	None	None	None	None
Jeffrey Hyman	Tricare Management Activity	None	None	None	None	None	None	None
Wolfgang Koenig	University of Ulm Medical Center (Germany)	None	None	None	None	None	None	None
Lauren L. Patton	University of North Carolina	None	None	None	None	None	None	None
Maurizio Tonetti	European Research Group on Periodontology (Switzerland)	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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Circulation. 2012;125:2520-2544; originally published online April 18, 2012;
doi: 10.1161/CIR.0b013e31825719f3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539