Journal of Periodontology and The American Journal of Cardiology; Copyright 2009

DOI: 10.1902/jop.2009.097001

Roundtable Discussion/Periodontitis and Atherosclerotic CVD

The American Journal of Cardiology and *Journal of Periodontology* Editors' Consensus: Periodontitis and Atherosclerotic Cardiovascular Disease[†]

Vincent E. Friedewald, MD[a,*], Kenneth S. Kornman, DDS, PhD[b],

James D. Beck, PhD[c], Robert Genco, DDS, PhD[d], Allison Goldfine, MD[e], Peter Libby, MD[f], Steven Offenbacher, DDS, PhD, MMsc[g], Paul M. Ridker, MD, MPH[h], Thomas E. Van Dyke, DDS, PhD[i], William C. Roberts, MD[j]

[a]Associate Editor, *The American Journal of Cardiology,* Research Professor, University of Notre Dame, Notre Dame, Indiana, and Clinical Professor, Department of Internal Medicine, The University of Texas Medical School at Houston, Houston, Texas; [b]Editor-in-Chief, *Journal of Periodontology,* and Chief Scientific Officer, Interleukin Genetics, Waltham, Massachusetts; [c]Distinguished Professor and Associate Dean for Research, University of North Carolina School of Dentistry, Chapel Hill, North Carolina; [d]Distinguished Professor, Department of Oral Biology and Department of Microbiology, University at Buffalo, State University of New York, Amherst, New York; [e]Associate Professor, Harvard Medical School, and Section Head of Clinical Research, Joslin Diabetes Center, Boston, Massachusetts; [f]Chief, Cardiovascular Medicine, Brigham and Women's Hospital, and Malinckrodt Professor of Medicine, Harvard Medical School, Boston, Massachusetts; [g]Distinguished Professor of Periodontology and Dental Research, University of North Carolina, Chapel Hill, North Carolina; [h]Eugene Braunwald Professor of Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts; [i]Professor and Program Director, Postdoctoral Periodontology, and Director, Clinical Research Center, Boston University, Goldman School of Dental Medicine, Boston, Massachusetts; and [j]Editor-in-Chief, *The American Journal of Cardiology* and *Baylor University Medical Center Proceedings*, Executive Director

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009 DOI: 10.1902/jop.2009.097001

Baylor Heart and Vascular Institute, Baylor University Medical Center, and Dean, A. Webb Roberts Center for Continuing Medical Education of Baylor Health Care System, Dallas, Texas.

*Corresponding author: Tel: 574-631-6675; fax: 574-631-4505.

E-mail address: vfriedew@nd.edu (V.E. Friedewald).

†Published simultaneously in *The American Journal of Cardiology*.

Acknowledgment

This Editors' Consensus is supported by an educational grant from Colgate-Palmolive, Inc., New York, New York, and is based on a meeting of the authors held in Boston, Massachusetts, on January 9, 2009.

Disclosure

Dr. Friedewald has received honoraria for speaking from Novartis, East Hanover, New Jersey. Dr. Kornman is a full-time employee and shareholder of Interleukin Genetics, Waltham, Massachusetts, which owns patents on genetic biomarkers for chronic inflammatory diseases. Dr. Genco is a consultant to Merck. Dr. Ridker has received research support from AstraZeneca, Wilmington, Delaware; Novartis; Pfizer, New York, New York; Roche, Nutley, New Jersey; Sanofi-Aventis, Bridgewater, New Jersey; and Abbott Laboratories, Abbott Park, Illinois. Dr. Ridker has received nonfinancial research support from Amgen, Thousand Oaks, California. Dr. Ridker is a co-inventor on patents held by Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. Dr. Ridker is a research consultant for Schering-Plough, Kenilworth, New Jersey; Sanofi-Aventis; AstraZeneca; Isis, Carlsbad, California; Novartis; and Vascular Biogenics, Tel Aviv, Israel. Dr. Van Dyke is a co-inventor on patents held by Boston University, Boston, Massachusetts, that relate to inflammation control, including consulting fees. Dr. Roberts has received honoraria for speaking from Merck, Whitehouse Station, New Jersey; Schering-Plough; AstraZeneca; and Novartis. All other individuals in a position to control content disclosed no relevant financial relationships.

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009
DOI: 10.1902/jop.2009.097001

Introduction

The organization of the health professions into specialties and subspecialties according to body organs and systems is often more pragmatic than scientific. The human organism is a single unit composed of a seemingly infinite number of biologic processes so intertwined that abnormalities of almost any of its parts or processes have profound effects on multiple other body areas, exemplified in this document by the common and complex theme of *inflammation*. In recent years, the immune system, once believed to be only a vital defense against infection and a promoter of healing—except in the instances of a few uncommon connective tissue disorders—is now recognized as a significant active participant in many chronic diseases, including hypertension, diabetes mellitus, arthritis, inflammatory bowel disease, psoriasis, and the 2 diseases addressed in this Editors' Consensus: atherosclerotic cardiovascular disease (CVD) and periodontitis.

This aim of this document is to provide health professionals, especially cardiologists and periodontists, a better understanding of the link between atherosclerotic CVD and periodontitis and, on the basis of current information, an approach to reducing the risk for primary and secondary atherosclerotic CVD events in patients with periodontitis.

Periodontitis, a bacterially induced, localized, chronic inflammatory disease, destroys connective tissue and bone that support the teeth. Periodontitis is common, with mild to moderate forms affecting 30% to 50% of adults and the severe generalized form affecting 5% to 15% of all adults in the United States.[1] Periodontitis has even higher prevalence in developing countries and considerable global variation, although the prevalence of the severe generalized disease appears to be similar in most populations.[2]

Patients with periodontitis are often asymptomatic. When present, physical signs and symptoms are nonspecific and include (Figure 1) swollen gums that decompress, discolored gums, tender gums, bleeding gums (spontaneous or after brushing or flossing), long appearance of teeth (because of receded gums), increased spacing between teeth, pus between teeth and gums, loose teeth, change in tooth sensation when biting because of increased tooth mobility, bad taste, and halitosis (because of anaerobic infection). Patients

DOI: 10.1902/jop.2009.097001

with periodontitis who have spontaneous oral pain or pain on mastication often have complications of the disease, including abscesses and other oral mucosal and alveolar bone lesions.

The clinical diagnosis of periodontitis requires evaluation by a trained examiner and evidence of gingival inflammation, loss of connective tissue surrounding the teeth measured by clinical examination using a periodontal probe, and bone loss detected by radiography (Figure 2).

Although moderate to severe periodontitis may affect systemic inflammatory and immune markers (e.g., elevated blood levels of C-reactive protein [CRP]), such changes are either not captured by current standard laboratory test panels or are interpreted as nonspecific indicators of a chronic, low-grade, acute-phase inflammatory response. Patients with uncomplicated periodontitis have no systemic signs of infection, such as fever or leukocytosis.

Pathophysiology: Periodontitis begins with a microbial infection, followed by a host-mediated destruction of soft tissue caused by hyperactivated or primed leukocytes and the generation of cytokines, eicosanoids, and matrix metalloproteinases that cause clinically significant connective tissue and bone destruction.[3] Bacterial accumulations on the teeth are essential to the initiation and progression of periodontitis. Cells that mediate immunity, such as neutrophils, play a major role in the host response against invading periodontopathogenic microorganisms. When bacterial biofilms on the teeth are not disrupted on a regular basis, ecologic changes lead to the emergence of a small set of gram-negative anaerobic bacterial species, including *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia*, which consistently associate with periodontitis. These bacteria activate many host immunoinflammatory processes and disrupt host mechanisms involved in bacterial clearance and are considered pathogens in periodontitis. Environmental and genetic factors as well as acquired risk factors such as diabetes mellitus and exposure to tobacco accelerate inflammatory processes in periodontitis. Although bacteria *initiate* periodontitis, host-modifying risk factors appear to influence the severity and extent of disease.

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009 DOI: 10.1902/jop.2009.097001

Risk factors (nonoral): The following nonoral risk factors associate strongly with increased risk for periodontitis and disease severity: smoking, diabetes mellitus, genetics, mental anxiety, depression, obesity, and physical inactivity.

Individuals who smoke (cigarettes and pipes) have 6 to 7 times more alveolar bone loss than nonsmokers in studies in the United States and other countries.[4–7] Patients with periodontitis defined by tooth attachment loss are 3 to 5 times more likely to smoke than those without attachment loss.[8] Possible mechanisms for the smoking-periodontitis relation include increased subgingival infection by periodontal pathogens,[9] increased smoking-induced proinflammatory circulating cytokine levels such as tumor necrosis factor–",[10] and altered collagen metabolism and wound healing.

Periodontal disease is more severe and prevalent in patients with type 1 and type 2 diabetes mellitus, on the basis of multiple domestic and global epidemiologic and clinical studies.[11] A large-scale longitudinal epidemiologic study in Pima Indians reported that the incidence of new cases of periodontitis in patients with type 2 diabetes in this ethnic population was >2.5 times greater than in nondiabetic subjects.[12] Patients with type 2 diabetes mellitus also have a faster rate of alveolar periodontal bone loss than those without diabetes with periodontitis.[13] Patients aged 10 to 18 years with type 1 diabetes mellitus have an increased prevalence of periodontitis.[14] In children and teens with diabetes, accelerated periodontal destruction relates to metabolic control.[15] Conversely, worsening periodontal disease adversely affects glycemic control.[11,13] It has been suggested that inflammation may be 1 mechanistic link between the 2 diseases.[13] Treatment of periodontal disease, especially in patients with elevated glycosylated hemoglobin, improves glycemic control.[16,17] Results from the National Health and Nutrition Examination Survey (NHANES) I and its follow-up studies suggest that nondiabetic adults with periodontal disease develop type 2 diabetes more often than those without periodontal disease.[18]

Approximately 50% of the variation in clinical severity of chronic periodontitis is explainable by genetic influences.[19] The first report of association with specific gene variants involved the interleukin (IL)–1 gene cluster,[12] but other identified genetic factors also are likely to contribute to periodontitis.[1]

DOI: 10.1902/jop.2009.097001

Treatment: All appropriate treatment strategies for periodontitis focus on the resolution of gingival inflammation and healing of the soft and hard tissue attachment of the teeth to the alveolar process by removal of the bacterial biofilm attached to the tooth roots and reinforcement of patient oral hygiene to reduce bacterial regrowth.

Systemic antibiotics may be used as an adjunct to conventional bacterial removal in severe periodontitis and in patients with host-modifying risk factors, such as diabetes mellitus.[20] Antibiotics locally delivered into the periodontal pockets have been approved by the United States Food and Drug Administration (FDA) as an adjunct to conventional bacterial removal in the management of periodontitis. Antibiotics markedly reduce the bacterial load but taken alone do not usually eliminate periodontal pathogens in the oral cavity. Antibiotics may transiently improve localized sites of periodontitis when combined with mechanical debridement to disrupt the subgingival biofilm.

Host-modulating drugs that reduce the clinical signs and symptoms and progression of periodontitis have been evaluated, and the matrix metalloproteinase inhibitor low-dose *doxycycline* is the only FDA-approved host-modulating drug for the treatment of periodontitis. Other host-modulating agents that hold promise but are not currently approved for use in periodontal therapy include nonsteroidal anti-inflammatory drugs (systemic [flurbiprofen] and topical [ketorolac]), bisphosphonates (alendronate sodium), and resolvins.

Advanced periodontitis (moderate to severe bone loss and gingival pocket depth >5 mm) may require surgery to gain adequate access for removal of the bacterial biofilm and residual calculus on the root surfaces. In some instances, surgical approaches include bone and soft tissue regeneration to regain at least some support for the teeth and to facilitate bacterial control.

Prevention: Long-term clinical studies have clearly demonstrated that the regular and effective removal of bacterial biofilms on the teeth can prevent periodontitis.[21] Effective removal requires excellent oral hygiene, including interproximal cleaning and periodic professionally administered biofilm removal.[22,23]

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009
DOI: 10.1902/jop.2009.097001

Inflammation and Atherosclerotic Cardiovascular Disease

The dietary ingestion of low-density lipoprotein (LDL), mainly from animal fat, with subsequent lipid oxidation and accumulation of lipid products within the arterial vascular wall is essential for atherogenesis. Thus, the most important current strategies for preventing atherosclerotic CVD are dietary fat restriction and pharmacologic measures that lower serum levels of LDL cholesterol. A number of risk factors also relate closely to the development of atherosclerotic disease and risk for cardiovascular events (e.g., myocardial infarction and stroke), including age, gender, hypertension, diabetes mellitus, smoking, and low serum levels of high-density lipoprotein (HDL) cholesterol.[24,25]

Over the past 2 decades, inflammation has emerged as an integrative CVD factor. Inflammation can operate in "all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis."[26] Higher quantiles of CRP, measured by a high-sensitivity assay (hsCRP), predict future acute myocardial infarction and unstable angina pectoris[27,28] and the onset of systemic arterial hypertension, diabetes mellitus, and stroke,[29–31] independent of blood lipid levels.[32] CRP itself, beyond serving as a biomarker, may have a role in endothelial cell dysfunction.[32–34] The erythrocyte sedimentation rate, chemokines, and cytokines including IL-6, IL-8, IL-10, IL-18, tumor necrosis factor–", and monocyte chemoattractant protein–1 also are frequently abnormal in patients with acute coronary syndromes[35–37] and in many other conditions. The incidence of atherosclerotic CVD events increases in patients with chronic inflammatory diseases, in addition to periodontitis, including rheumatoid arthritis,[38] psoriasis,[39] systemic lupus erythematosus,[40,41] and some types of infections, mainly infections of the respiratory tract and urinary tract.[42] Arterial inflammation, along with arterial stiffness and remodeling, may be a factor in systemic arterial hypertension,[43–53] particularly in obese patients. Evidence supporting the role of inflammation in atherosclerotic events gained support with the findings of Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER),[54] in which treatment with rosuvastatin significantly reduced the incidence of cardiovascular events in subjects with lower levels of LDL cholesterol but with mild

DOI: 10.1902/jop.2009.097001

chronic inflammation indicated by levels of hsCRP >2 mg/L. The precise role of inflammation as a *direct*, *causative* factor in chronic atherogenesis and in the acute complications of atherosclerosis remain an area of intense current investigation.[34,55,56]

Periodontitis and Atherosclerotic Cardiovascular Disease

The association between periodontitis and atherosclerotic CVD has received considerable attention.[57–90] The findings of these studies, however, have varied greatly, ranging from determinations of no causative relation between periodontitis and CVD to strong causative connections between the 2 conditions. Reasons for the discrepancies in the results of these studies include[72] (1) variations in study populations, including differing age groups, ethnicities, and geographic locations, and (2) differing measures and definitions of periodontitis, with some studies based only on clinical measures (i.e., pocket depth, bleeding with probing, tooth attachment level) and other studies, in which the relation appeared stronger, based on nonclinical measures such as systemic antibody response[70] or radiographic evidence of alveolar bone loss. Increased carotid artery intimal medial thickness measured by ultrasound, which is associated with increased risk for acute myocardial infarction and stroke in subjects without histories of CVD,[75] often occurs in patients with periodontitis, suggesting that subclinical atherosclerosis is present in many patients with periodontitis.[76,77]

Coronary artery disease (CAD): Although some past studies have not supported a causal relation between periodontitis and CAD,[76,86] a meta-analysis[91] of data linking CAD and periodontitis concluded that periodontal disease is a risk factor or marker independent of traditional CAD risk factors, with relative risk estimates ranging from 1.24 to 1.35. Another meta-analysis[92] also found significantly increased prevalence and incidence of CAD in patients with periodontitis, again raising the possibility that periodontitis independently predicts CAD. The 2 meta-analyses concluded, however, that further studies are needed to better define the relation between the 2 diseases. Analysis of >1,200 men in the Veterans Affairs Normative Aging and Dental Longitudinal Studies[61] determined that in men aged <60 years, there was a “significant dose-dependent

DOI: 10.1902/jop.2009.097001

association" between CAD prevalence and periodontitis, with a hazard ratio of 2.12 (95% confidence interval 1.26 to 3.30) when using clinical and radiographic criteria for periodontitis. This association was independent of standard atherosclerotic CVD risk factors or socioeconomic status. In men aged >60 years, however, the dose-dependent association between CAD and periodontitis was absent in this study. Periodontitis prevalence also has been correlated with angiographic evidence of CAD.[62]

Cerebrovascular disease: Analysis of NHANES I[93,94] and the NHANES Epidemiologic Follow-Up Study (NHEFS)[95] found that periodontal disease is an important risk factor for all forms of cerebrovascular disease, especially nonhemorrhagic stroke. Data from the Health Professionals Follow-Up Study (HPFS), which involved >50,000 male health professionals, revealed that periodontal disease and fewer teeth at baseline correlated with increased risk for stroke during the subsequent 12-year follow-up period.[96] Some studies, however, have not found a relation between periodontitis and cerebrovascular disease.[2,76]

Peripheral arterial disease: A small study reported a direct link between peripheral arterial disease and periodontitis, which related the 2 conditions in association with increases in the serum cytokines IL-6 and tumor necrosis factor–".[97] Another study of peripheral arterial disease in 212 young women (mean age 48 ± 7 years) found an independent relation between peripheral arterial disease and a history of periodontitis, unaffected by the level of hsCRP.[98]

Mechanisms for an Association Between Periodontitis and Atherosclerotic Cardiovascular Disease

A *direct* causal relation between periodontitis and atherosclerotic CVD is not established. Multiple studies, however, support 2 biologically plausible mechanisms[99–102]: (1) Moderate to severe periodontitis increases the level of systemic inflammation, a characteristic of all chronic inflammatory diseases, and periodontitis has been associated with increased systemic inflammation as measured by hsCRP and other biomarkers. Treatment of moderate to severe periodontitis sufficient to reduce clinical signs of the disease also

DOI: 10.1902/jop.2009.097001

decreases the level of systemic inflammatory mediators.[100,101] (2) In untreated periodontitis, 10^8 to 10^{12} gram-negative bacteria may be found in periodontal pockets surrounding each diseased tooth and in approximation to ulcerated epithelium, and bacterial species found predominantly in the periodontal pockets also have been found in atheroma.[102]

An *indirect* relation between periodontitis and atherosclerotic CVD is the many shared risk factors that commonly occur in the 2 diseases. Thus, many factors, especially cigarette smoking,[5–10] are confounders in determining their relative importance in this relation. There is evidence that periodontal disease is related to CVD in young (aged ≤55 years) nonsmokers.[90] In addition to tobacco use, the following risk factors are common to periodontitis and CVD: (1) Diabetes mellitus: there are no reported interventional studies designed to ascertain whether periodontal disease prevention or treatment reduces CVD prevalence or mortality in patients with either type 1 or type 2 diabetes mellitus. (2) Obesity: systemic inflammation, defined by increased circulating tumor necrosis factor–", is associated with obesity and periodontitis and has been proposed as a mechanism for the connection between these conditions.[103–106] Systemic inflammatory responses also could explain the association between periodontitis and type 2 diabetes by cytokine-induced insulin resistance. (3) Lipids: a case-controlled study showed that periodontitis is associated with elevated plasma triglycerides and total cholesterol.[107] A large epidemiologic study in the United States determined that total serum cholesterol and plasma levels of CRP and fibrinogen are elevated in patients with periodontitis.[86] Other epidemiologic studies in Japan[106] and Germany[107] also found that dyslipidemia is more common in patients with periodontitis. (4) Hypertension: an epidemiologic study in Sweden of >4,000 subjects showed an increased prevalence of hypertension in patients with periodontitis.[108] Smaller studies in the United States found that, after adjusting for confounders, hypertension was more prevalent in patients with severe alveolar bone loss,[109] and significantly more hypertension occurs in patients with periodontitis compared with populations with little or no periodontal disease.[110] Whether hypertension is a risk factor for periodontitis, however, remains uncertain. Systemic inflammation, a feature of hypertension, as evidenced by increased hsCRP plasma levels in patients with prehypertension and patients with established hypertension,[31] may link

DOI: 10.1902/jop.2009.097001

these 2 conditions.

Major depression, physical inactivity, family histories of CVD and periodontal disease, advancing age, and male gender are other risk factors for atherosclerotic CVD that are commonly found in patients with periodontitis and also may serve as confounders.

Clinical Recommendations: Patients With Periodontitis

Although the treatment of periodontitis reduces systemic markers of inflammation and endothelial dysfunction, no prospective periodontitis intervention studies have evaluated CVD outcomes. It seems reasonable, however, on the basis of current data, to acknowledge that because untreated or inadequately controlled moderate to severe periodontitis increases the systemic inflammatory burden, periodontitis *may* independently increase the risk for CVD. (See Table 1 for confidence and evidence level codes.)

I. Patient Information

Recommendation A: **Patients with moderate to severe periodontitis should be informed that there may be an increased risk for atherosclerotic CVD associated with periodontitis.**

Confidence and evidence level: 2C

Recommendation B: **Patients with moderate to severe periodontitis who have 1 known major atherosclerotic CVD risk factor, such as smoking, immediate family history of CVD, or history of dyslipidemia, should consider a medical evaluation if they have not done so in the past 12 months.**

Confidence and evidence level: 3D

Recommendation C: **Patients with periodontitis who have ≥2 known atherosclerotic CVD major risk factors should be referred for medical evaluation if they have not done so in the past 12 months**.

Confidence and evidence level: 2D

II. Medical and Dental Evaluations

In concert with the following recommendations, it is recommended that patients with periodontitis assess their risk for future (next 10 years) CVD events (e.g., stroke, myocardial infarction) by completing

DOI: 10.1902/jop.2009.097001

either the Reynolds Risk Score[111] (http://www.reynoldsriskscore.org) or, for risk assessment for CAD events only, the National Cholesterol Education Program Risk Calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof), based on the Framingham Heart Study.

Recommendation A: **Medical evaluation of patients with periodontitis should include assessment of atherosclerotic CVD risk, including past CVD events, and family histories of premature atherosclerotic CVD disease or sudden coronary death, diabetes mellitus, systemic hypertension, or dyslipidemia.**

Confidence and evidence level: 2D

Recommendation B: **Medical evaluation of patients with periodontitis should include a complete physical examination and annual measurement of blood pressure at rest (seated for 5 minutes with the feet on the floor and attention to appropriate blood pressure cuff size).**

Confidence and evidence level: 2D

Recommendation C: **Medical evaluation of patients with periodontitis should include a blood lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and fasting triglycerides) and blood glucose measurement. A plasma hsCRP determination is optional but should be considered, because recent studies have suggested that elevated plasma hsCRP may have added value by helping determine how aggressively standard risk factors should be treated, especially lifestyle changes.**[56,112,113]

Confidence and evidence level: 2D

III. Risk Factor Treatment: Abnormal Lipids

Recommendation A: **Patients with periodontitis and ≥1 abnormal serum lipid and/or elevated plasma hsCRP are recommended to follow a multifaceted lifestyle approach to reduce atherosclerotic CVD risk according to the National Cholesterol Education Program Adult Treatment Panel III guidelines.[114]**

Confidence and evidence level: 1C

According to Adult Treatment Panel III guidelines, emphasis on weight loss and physical activity to

DOI: 10.1902/jop.2009.097001

enhance weight reduction in subjects with elevated serum LDL cholesterol should be undertaken. Goals for LDL cholesterol levels are based on CVD risk assessment: (1) 1 atherosclerotic CVD risk factor and LDL cholesterol >160 mg/dl: target LDL cholesterol <160 mg/dl; (2) ≥2 atherosclerotic CVD risk factors and LDL cholesterol >130 mg/dl: target LDL cholesterol <130 mg/dl; an optional target is LDL cholesterol <100 mg/dl if factors such as age, metabolic syndrome, abnormal plasma hsCRP, or abnormal coronary calcium score (75th percentile) are present; (3) atherosclerotic CVD disease is present or there are CAD risk equivalents, such as diabetes mellitus: target LDL cholesterol <100 mg/dl or an optional target of <70 mg/dl if atherosclerotic CVD is present and there are high-risk features, such as diabetes mellitus, metabolic syndrome, heavy cigarette smoking, or acute coronary syndromes.

Lifestyle changes that should be undertaken are reduced intake of saturated fats (<7% of total calories) and low levels of trans fats and dietary cholesterol (<200 mg/day); enhancement of LDL lowering with optional dietary strategies, such as ingesting plant stanols or sterols (2 g/day) and increased viscous (soluble) fiber (10 to 25 g/day); weight reduction; increased physical activity; and limited alcohol ingestion ("*Moderation* is defined as the consumption of up to 1 drink per day for women and up to 2 drinks per day for men. Twelve fluid ounces of regular beer, 5 fluid ounces of wine, or 1.5 fluid ounces of 80-proof distilled spirits count as one drink. This definition of moderation is not intended as an average over several days but rather as the amount consumed on any single day."[114]) However, alcohol does not add to atherosclerotic CVD risk and may convey some protective effect against future CVD events. Patients who need to lose weight should be cautioned, however, that alcohol is high in caloric content. Subjects who do not drink alcohol should not be advised to begin drinking alcohol for the purpose of CVD risk modification, because other risks of alcohol consumption, such as higher frequencies of accidents and medical illnesses, outweigh the possible CVD-preventive benefits of alcohol.

Recommendation B: **Drug therapy for elevated LDL cholesterol should be prescribed in patients with periodontitis in whom target LDL cholesterol levels are not achieved with lifestyle changes.**

Confidence and evidence level: 2D

DOI: 10.1902/jop.2009.097001

IV. Risk Factor Treatment: Cigarette Smoking

Recommendation: **All patients with periodontitis who smoke tobacco should discontinue this habit because this is a major risk factor for atherosclerotic CVD and periodontitis.**

Confidence and evidence level: 1C

V. Risk Factor Treatment: Hypertension

Recommendation A: **All patients with periodontitis and elevated blood pressure should be treated to target levels as defined by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7).[24]**

Confidence and evidence level: 1C

JNC-7 defines hypertension as follows: (1) *prehypertension*: systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg; (2) *stage 1 hypertension*: systolic blood pressure 140 to 159 mm Hg or diastolic blood pressure 90 to 99 mm Hg; and (3) *stage 2 hypertension*: systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg. Using JNC-7 recommendations, the target blood pressures in patients with periodontitis are (1) <140/90 mm Hg in all patients with periodontitis and ≤2 major risk factors for CAD and (2) <130/80 mm Hg in patients with previous atherosclerotic CVD, diabetes mellitus, chronic renal disease, or ≥3 major risk factors.

Recommendation B: **All patients with periodontitis and elevated blood pressure should undertake lifestyle changes**.

Confidence and evidence level: 1A

Elevated blood pressure can be significantly decreased by lifestyle changes, including (pressures in parentheses indicate changes that can be anticipated with adequate patient compliance) weight reduction in subjects who are overweight (systolic blood pressure reduction 5 to 20 mm Hg), a diet high in potassium and calcium (the American Heart Association DASH diet[115] ; systolic blood pressure reduction 4 to 8 mm Hg), a diet low in sodium (systolic blood pressure reduction 2 to 8 mm Hg), physical activity (systolic blood pressure reduction 4 to 9 mm Hg), and moderation of alcohol intake (systolic blood pressure reduction 2 to 4 mm Hg).

DOI: 10.1902/jop.2009.097001

In addition to lowering blood pressure, lifestyle modifications also increase the efficacy of antihypertensive drug therapy and decrease the risk for atherosclerotic CVD.

Recommendation C: **All patients with periodontitis and elevated blood pressure not controlled to target levels with lifestyle changes should be treated with pharmacologic therapy.**

Confidence and evidence level: 2D

The following drug classes are approved for the initial treatment of hypertension: thiazide-type diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, $ blockers, and calcium channel blockers (see recommendation D).

Recommendation D: **Patients with periodontitis prescribed calcium channel blockers for hypertension or any other indication should be monitored for worsening of periodontitis in association with gum hyperplasia.**

Confidence and evidence level: 1D

Gingival hyperplasia has been reported with all 3 classes of calcium channel blockers.[116] This effect is reported most often with nifedipine, occurring in up to 6% of patients,[117] and less often with diltiazem, amlodipine,[118,119] and verapamil.[120,121] The mechanism is unknown but may be due to increased gingival collagen production by fibroblasts.[122] However, there are no specific reports of the effect of calcium channel blockers on the severity of periodontitis.

VI. Risk Factor Treatment: Metabolic Syndrome

Metabolic syndrome is diagnosed when ≥3 of the following features are present: (1) increased waist circumference (men ≥40 in [≥102 cm], women ≥35 in [≥88 cm]), (2) increased serum triglyceride level (150 mg/dl [1.7 mmol/L]) and/or drug treatment for elevated triglycerides (most commonly fibrates and nicotinic acid), (3) decreased serum HDL cholesterol level (men <40 mg/dl [1.03 mmol/L], women <50 mg/dl [1.3 mmol/L]) and/or drug treatment for decreased serum HDL cholesterol, (4) elevated blood pressure (≥130 mm Hg systolic and/or ≥85 mm Hg diastolic or antihypertensive drug treatment of patients with histories of hypertension, and (5) elevated fasting glucose (blood glucose ≥100 mg/dl and/or drug treatment for

DOI: 10.1902/jop.2009.097001

hyperglycemia).

Recommendation: **Patients with periodontitis meeting criteria for metabolic syndrome should be identified, and all risk factors for atherosclerotic CVD should be treated, beginning with lifestyle changes aimed at weight reduction.**

Confidence and evidence level: 1D

Metabolic syndrome is closely linked to insulin resistance and is a secondary target of lipid therapy because the risk factors for metabolic syndrome are highly concordant and, in aggregate, enhance the risk for atherosclerotic CVD at any serum level of LDL cholesterol.[123] *Many patients with periodontitis meet criteria for the metabolic syndrome*.[104] Because measures of systemic inflammation are a common feature of periodontitis and metabolic syndrome, it may be particularly important to identify patients who meet these criteria for CVD prevention strategies.

VII. Special Considerations in the Treatment of Atherosclerotic CVD in Patients With Periodontitis

No reported studies present evidence that patients with periodontitis and atherosclerotic CVD should receive different treatment from other patients with CVD, with the possible exception of the use of calcium channel blockers. Recent studies suggest that standard treatments of periodontitis in patients with CVD are effective.[124] The panel did make special note that additional studies are needed regarding the effect of other drugs used in cardiovascular medicine on periodontitis. There is, however, no conceptual basis for concern that any current standard treatment for periodontitis should be altered in patients with concurrent atherosclerotic CVD.

Clinical Recommendations: Patients With Atherosclerotic Cardiovascular Disease With or Without a Previous Diagnosis of Periodontitis

I. Patients With Atherosclerotic CVD and *Previous* Diagnosis of Periodontitis

Recommendation: **Periodontists and physicians managing patients with CVD should closely**

DOI: 10.1902/jop.2009.097001

collaborate to optimize CVD risk reduction and periodontal care.

Confidence and evidence level: 1D

II. Patients With Atherosclerotic CVD and *No Previous* Diagnosis of Periodontitis

Recommendation A: **Periodontal evaluation should be considered in patients with atherosclerotic CVD who have signs or symptoms of gingival disease, significant tooth loss, and unexplained elevations of hsCRP or other inflammatory biomarkers.**

Confidence land evidence level: 2D

Recommendation B: **Periodontal evaluation of patients with atherosclerotic CVD should include a comprehensive examination of periodontal tissues, as assessed by visual signs of inflammation and bleeding on probing, loss of connective tissue attachment detected by periodontal probing measurements, and bone loss assessed radiographically. If patients have untreated or uncontrolled periodontitis, they should be treated with a focus on reducing and controlling the bacterial accumulations and eliminating inflammation.**

Confidence and evidence level: 2D

Recommendation C: **When periodontitis is newly diagnosed in patients with atherosclerotic CVD, periodontists and physicians managing patients' CVD should closely collaborate to optimize CVD risk reduction and periodontal care.**

Confidence and evidence level: 1D

Recommendations for Future Research

Although the inflammation hypothesis provides a plausible and attractive explanation for the periodontitis-atherosclerosis relation, further research is needed to define the mechanisms linking the 2 diseases and how patients with periodontitis should best be managed to reduce their risk for CVD. Specific questions that the consensus panel believes should be addressed in future research include the following: (1) Is periodontitis an independent risk factor for atherosclerotic CVD? (2) If periodontitis is an independent risk

DOI: 10.1902/jop.2009.097001

factor for atherosclerotic CVD, what is the mechanism of the relation, and at what stage(s) of atherogenesis is it important? (3) Regardless of whether periodontitis is an independent risk factor for atherosclerotic CVD, should risk factors for atherosclerotic CVD be treated more aggressively in patients with periodontitis than current guidelines recommend for the general population? (4) Do periodontal therapeutic interventions, such as infection and inflammation control, directly reduce the rate of atherosclerotic plaque development and its complications, especially acute myocardial infarction and stroke? (5) Because periodontitis in the general population is greatly underdiagnosed and undertreated, what measures can improve its detection and management in persons at increased risk for primary and secondary atherosclerotic CVD events? (6) Are there specific oral microbial pathogens that add to CVD risk and therefore should be targeted for antibiotic treatment? (7) In addition to the possible role of periodontal inflammation caused by infection, does secondary endotoxemia play a causative role in the relation between periodontitis and atherosclerotic CVD? (8) Are acute events such as acute myocardial infarction and stroke more likely to occur during periods of worsening periodontitis? (9) Do calcium channel blockers have any adverse effect on periodontitis other than causing gingival hyperplasia in some persons, and if so, what is the magnitude of this effect? (10) In addition to calcium channel blockers, are there other cardiovascular medications that may adversely affect periodontitis?

1. American Academy of Periodontology. Epidemiology of periodontal diseases (position paper). *J Periodontol* 2005;76:1406–1419.

2. Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet* 2005;366:1809–1820.

3. Kornman KS, Page RC, Tonetti MS. The host response to the microbial challenge in periodontitis: assembling the players. *Periodontol 2000* 1997;14:33–53.

4. Westfelt E. Rationale of mechanical plaque control. *J Clin Periodontol* 1996;23:263–267.

5. Bergström J, Preber H. Tobacco use as a risk factor. *J Periodontol* 1994;65(suppl):545–550.

6. Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, Zambon JJ, Hausmann E. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. *J Periodontol* 1995;66:23–29.

DOI: 10.1902/jop.2009.097001

7. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. *J Periodontol* 2000;71:743–751.

8. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, Norderyd OM, Genco RJ. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *J Periodontol* 1994;65:260–267.

9. Zambon JJ, Grossi SG, Machtei EE, Ho AW, Dunford R, Genco RJ. Cigarette smoking increases the risk for subgingival infection with periodontal pathogens. *J Periodontol* 1996;67(suppl):1050–1054.

10. Makino A, Yamada S, Okuda K, Kato T. Nicotine involved in periodontal disease through influence oncytokine levels. FEMS Immunol Med Microbiol 2008;52:282–286.

11. Taylor GW, Borgnakke WS. Periodontal disease: associations with diabetes, glycemic control and complications. *Oral Dis* 2008;14:191–203.

12. Nelson RG, Shlossman M, Budding LM, Pettitt D, Saad MF, Genco RJ, Knowler WC. Periodontal disease and NIDDM in Pima Indians. *Diabetes Care* 1990;13:836–840.

13. Taylor GW, Burt BA, Becker MP, Genco RJ, Shlossman M, Knowler WC, Pettitt DJ. Non-insulin dependent diabetes mellitus and alveolar bone loss progression over 2 years. *J Periodontol* 1998;69:76–83.

14. Cianciola LJ, Park BH, Bruck E, Mosovich L, Genco RJ. Prevalence of periodontal disease in insulin-dependent diabetes mellitus (juvenile diabetes). *J Am Dent Assoc* 1982;104:653–660.

15. Lalla E, Cheng B, Lal S, Kaplan S, Softness B, Greenberg E, Goland RS, Lamster IB. Diabetes-related parameters and periodontal conditions in children. *J Periodontal Res* 2007;42:345–349.

16. Darré L, Vergnes JN, Gourdy P, Sixou M. Efficacy of periodontal treatment on glycemic control in diabetic patients: a meta-analysis of interventional studies. *Diabetes Metab* 2008;34:497–506.

17. Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ. treatment of periodontal disease in diabetics reduces glycated hemoglobin. *J Periodontol* 1997;68:713–719.

18. Demmer RT, Jacobs DR Jr, Desvarieux M. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. *Diabetes Care* 2008;31:1373–1379.

19. Michalowicz BS, Aeppli D, Virag JG, Klump DG, Hinrichs JE, Segal NL, Bouchard TJ Jr, Pihlstrom BL. Periodontal findings in adult twins. *J Periodontol* 1991;62:293–299.

20. Cionca N, Giannopoulou C, Ugolotti G, Mombelli A. Amoxicillin and metronidazole as an adjunct to full-mouth scaling and root planing of chronic periodontitis. *J Periodontol* 2009;80:364–371.

21. Axelsson P, Lindhe J. Effect of controlled oral hygiene procedures on caries and periodontal disease in adults. Results after 6 years. *J Clin Periodontol* 1981;8:239–248.

22. Axelsson P, Nyström B, Lindhe J. The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. *J Clin Periodontol* 2004;31:749–757.

23. Watt RG, Marinho VC. Does oral health promotion improve oral hygiene and gingival health?. *Periodontol 2000* 2005;37:35–47.

24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT, Roccella EJ; the National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252.

25. Ockene IS, Miller NH, for the American Heart Association Task Force on Risk Reduction. Cigarette smoking, cardiovascular disease, and stroke. *Circulation* 1997;96:3243–3247.

26. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135–1143.

27. Beer FC, Hind CR, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982;47:239–243.

28. Berk BC, Weintraub WS, Alexander RW. Elevation of C-reactive protein in “active” coronary artery disease. *Am J Cardiol* 1990;65:168–172.

29. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, Curhan GC, Rifai N, Cannuscio CC, Stampfer MJ, Rimm EB. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med* 2004;351:2599–2610.

30. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973–979.

31. Sesso HD, Buring JE, Rafai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003;290:2945–2951.

32. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007–2011.

33. Yeh ETH. CRP as a mediator of disease. *Circulation* 2004;109:II-11–II-14.

34. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit?. *Circulation* 2006;113:2128–2151.

35. Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes. *Circulation* 2006;113:72–75.

36. Inoue T, Komoda H, Nonaka M, Kameda M, Uchida T, Node K. Interleukin-8 as an independent predictor of long-term clinical outcome in patients with coronary artery disease. *Int J Cardiol* 2008;124:319–325.

37. Natali A, L'Abbate, Ferrannini E. Erythrocyte sedimentation rate, coronary atherosclerosis, and cardiac mortality. *Eur Heart J* 2003;24:639–648.

38. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, Sammaritano L, Devereux RB, Schwartz JE, Levine DM, Salmon JE. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;144:249–256.

39. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735–1741.

40. Asanuma Y, Oeser A, Shintani AK, Turner E, Olsen N, Fazio S, Linton MF, Raggi P, Stein CM. Premature coronary-artery atherosclerosisin systemic lupus erythematosus. *N Engl J Med* 2003;349:2407–2415.

41. McMahon M, Hahn BH. Atherosclerosis and systemic lupus erythematosus—mechanistic basis of the association. *Curr Opin Immunol* 2007;19:633–639.

42. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and

DOI: 10.1902/jop.2009.097001

stroke after acute infection or vaccination. *N Engl J Med* 2004;351:2611–2618.

43. Marchesi C, Paradis P, Schiffrin EL. Role of the renin-angiotensin system in vascular inflammation. *Trends Pharmacol Sci* 2008;29:367–374.

44. Sahar S, Dwarakanath RS, Reddy A, Lanting L, Todorov I, Natarajan R. Angiotensin II enhances interleukin-18 mediated inflammatory gene expression in vascular smooth muscle cells. *Circ Res* 2005;96:1064–1071.

45. Katariina K, Perola M, Terwilliger J, Kaprio J, Koskenvuo M, Syvänen A-C, Vartiaien E, Peltonen L, Kontula K. Evidence for involvement of the type 1 angiotensin II receptor locus in essential hypertension. *Hypertension* 1999;33:844–849.

46. Ferrario CM, Strawn WB. Role of renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. *Am J Cardiol* 2006;98:121–128.

47. Lim HS, Lip GYH. Interleukin-15 in hypertension: further insights into inflammation and vascular disease. *Am J Hypertens* 2005;18:1017–1018.

48. Kampus P, Muda P, Kals J, Ristimäe T, Fischer K, Teesalu R, Zilmer M. The relationship between inflammation and arterial stiffness in patients with essential hypertension. *Int J Cardiol* 2006;122:46–51.

49. Karthikeyan VJ, Lip GYH. Alpha 1-microglobulin: a further insight to inflammation in hypertension?. *Am J Hypertens* 2007;20:1022–1023.

50. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension* 2005;46:1118–1122.

51. Engström G, Janzon L, Berglund O, Lind P, Stavenow L, Hedblad B, Lindgärde F. Blood pressure increase and incidence of hypertension in relation to inflammation-sensitive plasma proteins. *Arterioscler Thromb Vasc Biol* 2002;22:2054–2058.

52. August P, Suthanthiran M. Transforming growth factor signaling, vascular remodeling, and hypertension. *N Engl J Med* 2006;354:2721–2723.

53. Lakoski SG, Herrington DM, Siscovick DM, Hulley SB. C-reactive protein concentration and incident

DOI: 10.1902/jop.2009.097001

hypertension in young adults. *Arch Intern Med* 2006;166:345–349.

54. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207.

55. Libby P, Ridker PM. Inflammation and atherothrombosis. *J Am Coll Cardiol* 2006;48:A33–A46.

56. Granger DN, Vowinkel T, Petnehazy T. Modulation of the inflammatory response in cardiovascular disease. *Hypertension* 2004;43:924–931.

57. Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, Van der Velden UV. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *J Periodontol* 2000;71:1528–1534.

58. Beck JD, Eke P, Heiss G, Madianos P, Couper D, Lin D, Moss K, Elter J, Offenbacher S. Periodontal disease and coronary heart disease: a reappraisal of the exposure. *Circulation* 2005;112:19–24.

59. Danesh J. Coronary heart disease, Helicobacter pylori, dental disease, Chlamydia pneumoniae, and cytomegalovirus: meta-analyses of prospective studies. *Am Heart J* 1999;138:S434–S437.

60. Persson GR, Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. *J Clin Periodontol* 2008;35(suppl):362–379.

61. Dietrich T, Jimenez M, Krall Kaye EA, Vokonas PS, Garcia RI. Age-dependent associations between chronic periodontitis/edentulism and risk of coronary heart disease. *Circulation* 2008;117:1668–1674.

62. Amabile N, Susini G, Pettenati-Soubayroux I, Bonello L, Gil J-M, Arques S, Bonfil JJ, Paganelli F. Severity of periodontal disease correlates to inflammatory systemic status and independently predicts the presence and angiographic extent of stable coronary artery disease. *J Intern Med* 2008;263:644–652.

63. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999;340:14–22.

64. Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease

to carotid artery intima-media wall thickness: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb Vasc Biol* 2001;21:1816–1822.

65. Cairo F, Castellani S, Gori AM, Nieri M, Baldelli G, Abbate R, Pini-Prato GP. Severe periodontitis in young adults is associated with sub-clinical atherosclerosis. *J Clin Periodontol* 2008;35:465–472.

66. Hujoel PP, Drangsholt M, Spiekerman C, DeRouen TA. Periodontal disease and coronary heart disease risk. *JAMA* 2000;284:1406–1410.

67. Kinane DF, Lowe GD. How periodontal disease may contribute to cardiovascular disease. *Periodontol 2000* 2000;23:121–126.

68. Herzberg MC, Meyer MW. Effects of oral flora on platelets: possible consequences in cardiovascular disease. *J Periodontol* 1996;67(suppl):1138–1142.

69. Sahingur SE, Sharma A, Genco RJ, de Nardin ED. Association of increased levels of fibrinogen and the -455G/A fibrinogen gene polymorphism with chronic periodontitis. *J Periodontol* 2003;74:329–337.

70. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20(suppl):21–35.

71. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. *BMJ* 1993;306:688–691.

72. Mattila KJ, Valtonen VV, Nieminen M, Huttunen JK. Dental infection and the risk of new coronary events: prospective study of patients with documented coronary artery disease. *Clin Infect Dis* 1995;20:588–592.

73. Joshipura KJ, Rimm EB, Douglass CW, Trichopoulos D, Ascherio A, Willett WC. Poor oral health and coronary heart disease. *J Dent Res* 1996;75:1631–1636.

74. Wu J, Trevisan M, Genco R, Dorn J, Falkner K, Sempos C. Periodontal disease as a risk factor for CVD, CHD, and stroke. *Circulation* 1999;99:1109–1125.

75. Howell TH, Ridker PM, Ajani UA, Hennekens CH, Christen WG. Periodontal disease and risk of subsequent cardiovascular disease in US male physicians. *J Am Coll Cardiol* 2001;37:445–450.

76. Loesche WJ, Schork A, Terpenning MS, Chen YM, Dominguez BL, Grossman N. Assessing the

relationship between dental disease and coronary heart disease in elderly US veterans. *J Am Dent Assoc* 1998;129:301–311.

77. Arbes SJ Jr, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. *J Dent Res* 1999;78:1777–1782.

78. Buhlin K, Gustafsson A, Håkansson J, Klinge B. Oral health and cardiovascular disease in Sweden. *J Clin Periodontol* 2002;29:254–259.

79. Buhlin K, Gustafsson A, Håkansson J, Klinge B. Self-reported oral health, dental care habits and cardiovascular disease in an adult Swedish population. *Oral Health Prev Dent* 2003;1:291–299.

80. Elter JR, Champagne CM, Offenbacher S, Beck JD. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. *J Periodontol* 2004;75:782–790.

81. Malthaner SC, Moore S, Mills M, Saad S, Sabatini R, Takacs V, McMahan A, Oates TW. Investigation of the association between angiographically defined coronary artery disease and periodontal disease. *J Periodontol* 2002;73:1169–1176.

82. Geerts SO, Legrand V, Charpentier J, Albert A, Rompen EH. Further evidence of the association between periodontal conditions and coronary artery disease. *J Periodontol* 2004;75:1274–1280.

83. Buhlin K, Gustafsson A, Ahnve S, Janszky I, Tabrizi F, Klinge B. Oral health in women with coronary heart disease. *J Periodontol* 2005;76:544–550.

84. Briggs JE, McKeown PP, Crawford VLS, Woodside JV, Stout RW, Evans A, Lindenet GJ. Angiographically confirmed coronary heart disease and periodontal disease in middle-aged males. *J Periodontol* 2006;77:95–102.

85. Spahr A, Klein E, Khuseyinova N, Boeckh C, Muche R, Markus K, Rothenbacher D, Pezeshki G, Hoffmeister A, Koeniget W. Periodontal infections and coronary heart disease: role of periodontal bacteria and importance of total pathogen burden in the Coronary Event and Periodontal Disease (CORODONT) study. *Arch Intern Med* 2006;166:554–559.

86. Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT. Examination of the relation between

DOI: 10.1902/jop.2009.097001

periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *Am J Epidemiol* 2000;151:273–282.

87. Glurich I, Grossi S, Albini B, Ho A, Shah R, Zeid M, Bauman H, Genco RJ, DeNardin E. Systemic inflammation in cardiovascular and periodontal disease: comparative study. *Clin Diagn Lab Immunol* 2002;9:425–432.

88. Andriankaja OM, Genco RJ, Dorn J, Dmochowski J, Hovey K, Falkner KL, Trevisn M. Periodontol disease and risk of myocardial infarction: the role of gender and smoking. *Eur J Epidemiol* 2007;22:699–703.

89. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk* 1999;6:7–11.

90. Luoto R, Pekkanen J, Uutela A, Tuomilehto J. Cardiovascular risks and socioeconomic status: differences between men and women in Finland. *J Epidemiol Commun Health* 1994;48:348–354.

91. Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand MJ. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. *Gen Intern Med* 2008;23:2079–2086.

92. Bahekar AA, Singh S, Saha S, Molnar J, Arora R. The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *Am Heart J* 2007;154:830–837.

93. Wu T, Trevisan M, Genco RJ, Dorn JP, Falkner KL, Sempos CT. Periodontal disease and risk of cerebrovascular disease: the First National Health and Nutrition Examination Survey and its follow-up study. *Arch Intern Med* 2000;160:2749–2755.

94. National Center for Health Statistics, Plan and Operation of the Health and Nutritional Examination Survey, United States, 1971-1973. Washington, District of Columbia: United States Government Printing Office, 1973.

95. National Center for Health Statistics. Plan and Operation of the NHANES 1 Epidemiological Follow-Up Study, 1992. Washington, District of Columbia: United States Government Printing Office, 1998.

96. Joshipura KJ, Hung H-C, Rimm EB, Willett WC, Ascherio A. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke* 2003;34:47–52.

97. Chen YW, Umeda M, Nagasawa T, Takeuchi Y, Huang Y, Inoue Y, Iwai T, Izumi Y, Ishikawa I. Periodontitis may increase the risk of peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2008;35:153–158.

98. Bloemenkamp DG, van den Bosch MA, Mali WP, Tanis BC, Rosendaal FR, Kemmeren JM, Algra A, Visseren FL, van der Graaf Y. Novel risk factors for peripheral arterial disease in young women. *Am J Med* 2002;113:462–467.

99. Linden GJ, McClean K, Young I, Evans A, Kee F. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. *J Clin Periodontol* 2008;35:741–747.

100. Haraszthy VI, Zambon JJ, Trevisan M, Zeid M, Genco RJ. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol* 2000;71:1554–1560.

101. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol* 2008;35:277–290.

102. Tonetti MS, D'Auito F, Nibali L, et al. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007;356:911–920.

103. Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* 2003;74:610–615.

104. Genco RJ, Grossi SG, Ho A, Nishimura F, Murayama Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J Periodontol* 2005;76(suppl):2075–2084.

105. Cutler CW, Shinedling EA, Nunn M, Jotwani R, Kim BO, Nares S, Iacopino AM. Association between periodontitis and hyperlipidemia: cause or effect?. *J Periodontol* 1999;70:1429–1434.

106. Morita M, Horiuchi M, Kinoshita Y, Yamamoto T, Watanabe T. Relationship between blood triglyceride levels and periodontal status. *Commun Dent Health* 2004;21:32–36.

107. Lösche W, Marshal GJ, Apatzidou DA, Krause S, Kocher T, Kinane DF. Lipoprotein-associated phospholipase A2 and plasma lipids in patients with destructive periodontal disease. *J Clin Periodontol* 2005;32:640–644.

108. Holmlund A, Holm G, Lind L. Severity of periodontal disease and number of remaining teeth are related

DOI: 10.1902/jop.2009.097001

to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. *J Periodontol* 2006;77:1173–1178.

109. Al-Emadi A, Bissada N, Farah C, Siegel B, Al-Zaharani M. Systemic diseases among patients with and without alveolar bone loss. *Quintessence Int* 2006;37:761–765.

110. Engstrom S, Gahnberg L, Hogberg H, Svardsudd K. Association between high blood pressure and deep periodontal pockets: a nested case-referent study. *Ups J Med Sci* 2007;112:95–103.

111. Ridker PM, Paynter NP, Rifai N, Gaziano JM, Cook NR. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation* 2008;118:2243–2251.

112. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol* 2005;45:1563–1569.

113. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol <70 mg/dl and C-reactive protein <2 mg/L: an analysis of the PROVE-IT TIMI-22 trial. *J Am Coll Cardiol* 2005;45:1644–1648.

114. Grundy SM, Cleeman JI, Mertz CN, Brewer HB, Clark LT, Huninghake DB, Pasternak RC, Smith SC, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–239.

115. National Institutes of Health. Your guide to lowering your blood pressure with DASH. Available at: http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_pdf. Accessed February 25, 2009.

116. Missouris GG, Kalaitzidis RG, Cappuccio FP, MacGregor GA. Gingival hyperplasia caused by calcium channel blockers. *J Hum Hypertens* 2000;14:155–156.

117. Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: a community-based study. *J Periodontol* 1999;70:63–67.

118. Routray SN, Mishra TK, Pattnaik UK, Satapathy C, Mishra CK, Behera M. Amlodipine-induced gingival hyperplasia. *J Assoc Physicians India* 2003;51:818-819.

DOI: 10.1902/jop.2009.097001

119. Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. *J Periodontol* 1997;68:676–678.

120. Matharu MS, van Vliet JA, Ferrari MD, Goadsby PJ. Verapamil induced gingival enlargement in cluster headache. *J Neurol Neurosurg Psychiatry* 2005;76:124–127.

121. Miller CS, Damm DD. Incidence of verapamil-induced gingival hyperplasia in a dental population. *J Periodontol* 1992;63:453–456.

122. Li B, Sun W, Yong J. The effect of nifedipine on the expression of type I collagen in gingival fibroblasts. *J Nanging Univ* 2008;22:92–95.

123. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Spertus JA, Costa F; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome. *Circulation* 2005;112:2735–2752.

124. Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, Couper DJ, Stewart DD, Falkner KL, Graham SP, Grossi S, Gunsolley JC, Madden T, Maupome G, Trevisan M, Van Dyke TE, Genco RJ. Results from the Periodontitis and Vascular Events (PAVE) study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *J Periodontol* 2009;80:190–201.

Figure 1. In this patient with untreated moderate periodontitis, changes in tissue contours and color are present *(A)*. The yellow-brown discolored areas of the teeth *(B)* are root surfaces that have been exposed with gingival recession due to destruction of the connective tissue attachment. The exposed root surfaces are covered with bacterial deposits, portions of which are calcified.

Figure 2. In periapical x-ray *A*, marginal bone levels *(line a)* are consistent with no history of periodontitis. In periapical x-ray *B*, periodontitis has caused resorption of approximately 50% to 60% of the bone supporting the mandibular anterior teeth. The approximate level of bone that would be expected in the absence of periodontitis is marked by *line a*, and the approximate level at the time of the x-ray is marked by *line b*.

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009 DOI: 10.1902/jop.2009.097001

Table 1 Confidence and evidence codes

Confidence	Description
1	Very confidant
2	Confident
3	Marginally confidant
4	Not confidant
	Type of evidence
A	Well-designed RCT conducted in patients who have reported adverse experiences
B	Single RCT with a highly statistically significant result
	Well-conducted retrospective case-control studies with adverse experiences as primary end points
	Managed care claims database analysis with a highly statistically significant result
C	Reports to regulatory agencies judged to exceed population averages and reporting bias
	Multiple case studies with nonblinded dechallenge and rechallenge
	Strong trends, not reaching statistical significance, for safety issues in large RCTs
	Well-conducted prospective cohort study, giving a result that is statistically well above population average
	Metabolic or clinical surrogate studies
D	Undocumented opinion of experienced research investigators and clinicians
	Poorly controlled or uncontrolled studies
	Nondefinitive evidence from regulatory agency reporting systems or managed care claims databases
U	Unknown, no appropriate evidence, or evidence considered subject to bias
RCT = randomized controlled trial.	

Journal of Periodontology and The American Journal of Cardiology; Copyright 2009
DOI: 10.1902/jop.2009.097001

Fig. 1

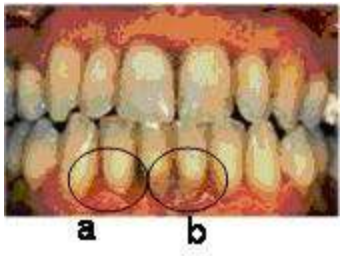

Fig. 2