Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2008; 35 (Suppl. 8): 362–379 doi: 10.1111/j.1600-051X.2008.01281.x

# Cardiovascular disease and periodontitis: an update on the associations and risk

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*Persson GR, Persson RE. Cardiovascular disease and periodontitis: an update on the associations and risk. J Clin Periodontol 2008; 35 (Suppl. 8): 362–379. doi: 10.1111/j.1600-051X.2008.01281.x.*

***Abstract***

**Background:** Associations between periodontitis and cardiovascular diseases have been recognized.

**Material and Methods:** New literature since the last European Workshop on Periodontology has been reviewed.

**Results:** The lack of reliable epidemiological data on disease prevalence makes an assessment of the associations and risks between periodontitis and cardiovascular diseases difficult. Two recent meta-analysis reports have identified associations between periodontitis and cardiovascular diseases (odds ratios: 1.1–2.2). Different surrogate markers for both disease entities, including serum biomarkers, have been investigated. Brachial artery flow-mediated dilatation, and carotid intima media thickness have in some studies been linked to periodontitis. Studies are needed to confirm early results of improvements of such surrogate markers following periodontal therapy. While intensive periodontal therapy may enhance inflammatory responses and impair vascular functions, studies are needed to assess the outcome of periodontal therapies in subjects with confirmed cardiovascular conditions. Tooth eradication may also reduce the systemic inflammatory burden of individuals with severe periodontitis. The role of confounders remain unclear.

**Conclusions:** Periodontitis may contribute to cardiovascular disease and stroke in susceptible subjects. Properly powered longitudinal case–control and intervention trials are needed to identify how periodontitis and periodontal interventions may have an impact on cardiovascular diseases.

Key words: acute coronary syndrome; atherosclerosis; infection; inflammation; periodontitis; review; stroke; therapy

Accepted for publication 20 May 2008

Cardiovascular diseases comprise a variety of heart and vascular conditions including: ischaemia, atherosclerosis, peripheral artery disease, infective endocarditis, and acute myocardial infarction (Karchmer 1997). Cardiovascular diseases are common in many adult populations (Rosamond et al. 2007). Over the last 30 years, the greater life expectancy and changes in diet and exercise habits have resulted in a higher prevalence of obesity, elevated levels of blood cholesterol, hypertension, and diabetes mellitus which are all recognized cardiovascular risk factors. Smoking is another risk factor in cardiovascular disease contributing to the increasing incidence and mortality of cardiovascular diseases (Kuller 2006).

Atherosclerosis, and myocardial infarctions occur as a product of complex combinations of factors (Ross 1997). Myocardial infarctions, stroke, and thromboembolic events result from atherosclerosis and often in combination with a superimposed coronary thrombosis. Development of atherosclerosis begins already in the first or second decade of life, and with clinical manifestations many years later.

A large number of surrogate endpoints of future cardiovascular diseases has been identified. This includes assessments of carotid intima media thickness (IMT), flow-mediated dilatation of the brachial artery, serum biomarkers including high density lipoprotein (HDL), low density lipoprotein (LDL), cholesterol fibrinogen, triglyceride, high sensitivity CRP, HbA1c, and systolic/diastolic blood pres-

**Conflict of interest and source of funding statement**

The Clinical Research Foundation for the Promotion of Oral Health (CRF) University of Berne, Switzerland has supported the review. The authors declare no conflict of interests.

The 6th European Workshop on Periodontology was supported by an unrestricted educational grant from Straumann AG.

sure. These surrogate measures, however, only partly account for the occurrence of future cardiovascular diseases (EUROASPIRE 1997). Currently, there are no recognized definitive diagnostic risk markers of cardiovascular diseases.

Diabetes mellitus constitutes another risk for cardiovascular disease and with a high mortality rate (Golden et al. 2007). Pro-inflammatory mediators implicated in hyperglycemia has also been associated with periodontitis and indicative of increased cardiovascular disease risks (Janket et al. 2007). A variety of processes may be responsible for coronary artery abnormalities. This includes diet/overweight, metabolic disease, lack of exercise, stress, drugs, socioeconomic status, gender, and genetic factors.

Many epidemiological studies have identified statistically significant associations between established Periodontitis and cardiovascular diseases (i.e. Mattila et al. 1989, DeStefano et al. 1993, Beck et al. 1996). This association is not without dispute (Hujoel et al. 2001, Beck et al. 2005). This review includes documents published between 2000 and December 2007, and with focus on the last 3 years seeking explanatory factors to why patients with periodontitis may be at an elevated risk for cardiovascular diseases. A literature search using Embase and Medline identified more than 550 peer-reviewed publications on cardiovascular diseases and periodontitis and published in many different languages. Publications ($>100$) in the Italian, French, German, Polish, Russian, and in Chinese languages were excluded in this review and only literature in the English language has been considered.

## Periodontitis-Cardiovascular Diseases – Association Studies

The relationship between periodontitis and cardiovascular disease has been summarized in two recent publications based on the principles of meta-analysis (Bahekar et al. 2007, Mustapha et al. 2007). The analysis by Bahekar et al. (2007) including five prospective cohort studies (86,092 patients) indicated that individuals with periodontitis had a 1.14 times higher risk of developing coronary heart disease than subjects without periodontitis [relative risk 1.14, 95% confidence interval (CI) 1.01–1.2, $p<0.001$]. The case–control studies (1423 patients) showed greater odds of an association between periodontitis and coronary heart disease [odds ratio (OR) 2.2, 95% CI 1.6–3.1, $p<0.001$]. The prevalence of coronary heart disease in the cross-sectional studies reviewed (17,724 patients) was greater among individuals with periodontitis than in subjects without periodontitis (OR 1.6, 95% CI: 1.3–1.9, $p<0.001$).

Table 1 provides a summary based on studies on the associations and risks between periodontitis and cardiovascular diseases. Meta-analysis of prospective and retrospective follow-up studies have shown that periodontal disease may only slightly increase the risk of cardiovascular disease (Meurman et al. 2003, Bahekar et al. 2007, Mustapha et al. 2007). Furthermore, when adjusting for demographic factors, studies have shown that the association between periodontitis based on clinical attachment level measurements in relation to coronary artery calcification (Agatason score) does not demonstrate a significant association between the two conditions (Nakib et al. 2004). In contrast, others have found a significant relationship between periodontal status based on clinical measures of probing pocket depth/clinical attachment loss and acute myocardial infarction (Cueto et al. 2005). Most studies provide odds ratios of periodontitis (defined by clinical measures of probing pocket depth and clinical attachment levels) as a risk for cardiovascular disease at levels less than a ratio of 3:1. Studies resulting in higher ORs have commonly used alveolar bone loss as the definition of periodontitis rather than measures of probing pocket depth and clinical attachment level (Persson et al. 2003a, Engebretson et al. 2005, Geismar et al. 2006, Rech et al. 2007). The study by Beck et al. (2005) confirmed that clinical signs (bleeding on probing, probing pocket depth, clinical attachment levels) are not representative for the impact of cumulative effects of periodontitis on systemic health. Disparities in prevalence rates of periodontitis in study populations with different age groups, ethnicity, and geographic location makes it difficult to assess the likelihood of an association between periodontitis and cardiovascular diseases.

Stroke is one of the major vascular diseases. An association between cerebrovascular events and periodontitis has been identified in a few studies (Persson et al. 2002, Grau et al. 2004). Doppler sonography of the carotid arteries is a routine measure of stroke risk. Carotid artery calcification can be seen on panoramic dental radiographs and can be related to a history of cerebral infarction (Kumagai et al. 2007). Studies have demonstrated that the accuracy of panoramic radiographs against current gold standard for the diagnosis of carotid coronary calcification (doppler sonography) is high (Ravon et al. 2003). Patients presenting with evidence of carotid calcification on panoramic radiographs should be referred for cerebro-vascular and cardiovascular evaluation and treatment (Cohen et al. 2002).

### Role of infection and immune response in periodontitis and cardiovascular disease

The role of infection in acute coronary syndrome, stroke, and atherosclerosis is disputed. An infectious burden may be less significant in cardiovascular disease development than previously thought (Steptoe et al. 2007). The hypothesis that different bacteria are involved in the development of atherosclerosis may also be an effect of the total infectious burden and not caused by a single bacterial infection (Espinola-Klein et al. 2002, Honda et al. 2005). In the case of infective endocarditis, a specific microbial infection of the endothelial surface of the heart and heart valves is more evident. A large number of different types of bacteria, fungi, and virus have been identified in infective endocarditis of subjects age 60+ (Karchmer 1997, Baldassarri et al. 2004, Presterl et al. 2005).

Several studies have investigated the role of infection in cardiovascular diseases.

Studies suggest that *Chlamydia pneumoniae* and *Helicobacter pylori* can be linked to cardiovascular diseases (Liu et al. 2006, Miyazaki et al. 2006, Nyström-Rosander et al. 2006, Atar et al. 2007). Nevertheless, there is no common agreement on the role of bacteria and infection as a primary etiology for cardiovascular diseases. The infectious etiology of periodontitis is, however, well established (Socransky & Haffajee 2005, Paster et al. 2006). Several studies assessing the presence of bacteria associated with periodontitis in specimens collected from the aorta or other blood vessels have identified bacteria associated with periodontitis in samples from aorta and heart valves. A summary of such reports is provided (Table 2).

*Table 1.* Studies assessing associations between cardiovascular diseases and periodontitis

| Authors | Study design | Periodontal diagnosis | Medical diagnosis | Association |
|---|---|---|---|---|
| Mattila et al. (1989) | Case–control study | Total dental index: caries, periodontitis, peri-apical lesions, abscess (14 criteria). Subjects were assigned a score from 0 to 10 | ACS consecutive cases, hospital confirmed cases | ACS-cholesterol ($p<0.001$)<br>ACS-detal index ($p<0.01$)<br>ACS-smoking ($p<0.01$)<br>Odds ratio was not calculated |
| DeStefano et al. (1993) | Epidemiological study based on the NHANES I and the (NHEFS) data | Russell index<br>Gingivitis<br>Periodontitis | Incidence of coronary heart disease (CHD) 1974–1987 | CHD-gingivitis:<br>OR = 0.95, 95% CI: 0.5–1.8<br>CHD-periodontitis:<br>OR = 1.5, 95% CI: 0.8–3.0<br>CHD = CHD-Russell index:<br>OR = 1.1, 95% CI: 0.9–1.3 |
| Beck et al. (1996) | A cohort study with combined data from (1) the Normative Aging Study, (2) the Dental Longitudinal Study (Veterans Affair) | Bone loss score based on 5 different categories was assessed. More than 20% sites with bone loss = periodontitis | Coronary heart disease including non-fatal infarction, angina pectoris, and coronary heart disease death | OR = 1.5<br>95% CI: 1.01 to 2.1 |
| Morrison et al. (1999) | A retrospective study 1972–1993, the Nutrition Canadian Survey | Oral health/periodontitis | Mortality experience in cornary heart disease | OR = 2.2<br>95% CI: 1.3 to 3.7 |
| Persson et al. (2002) | Cross-sectional study of older subjects 65+ | Composite of radiographic evidence and probing pocket depth | Self-reported history of cardiovascular diseases confirmed by medication lists | OR = 4.3 95% CI 2.4–7.9 |
| Lessem et al. (2002) | Retrospective case series | Radiographic evidence of alveolar bone loss | Heart transplant cases were searched through medical records | 76% of cases had periodontitis before heart transplantation. |
| Meurman et al. (2003) | Case–control study of 256 subjects with heart disease and 250 controls | Revised version of the dental index as described by Mattila et al., 1989 and based on clinical and radiological dental examinations (MDI index) | Serum samples of 256 patients with New York Heart Association class II–IV heart disease | High MDI/heart disease<br>OR = 1.3 95% CI: 1.2–1.5<br>Gingivitis/heart disease<br>(OR = 3.4, 95% CI: CI 1.7–6.9) |
| Persson et al. (2003c) | Matched case–control study based on consecutive cases of acute coronary syndrome | Alveolar bone loss $\geqslant 4$ mm at approximal sites<br>Different proportional rates from $<10\%$ to $>50\%$ of sites with alveolar bone loss | Acute coronary syndrome consecutive cases with hospital diagnosis. Age, gender, smoking status, socio-economic matched controls through medical examination | All subjects:<br>Bone loss $>50\%$<br>OR = 14.1 95% CI: 5.5–28.2<br>Bone loss $>30\%$ of sites<br>OR = 12.95% CI: 4.7–35.3<br>in non-smokers:<br>OR = 5.9 95% CI: 1.4–24.4 |
| Ravon et al. (2003) | Case–control study | Bone loss $\geqslant 4$ mm at approximal sites at $>30\%$ of sites | Positve or negative duplex ultrasonography | OR: 38.4, 95% CI: 10.6–138.7 |
| Geerts et al. (2004) | Case–control study 108 coronary heart disease cases and 62 healthy control subjects | Periodontitis defined by probing pocket depth . One site or more $\geqslant 5$ mm<br>New index for periodontal infection risk index (PIRI) | Hospital confirmed cases with coronary heart disease in treatment | OR: 6.5, 95% CI 1.8–23.0)<br>A dose response curve for the PIRI index and coronary heart disease |
| Nakib et al. (2004) | Epidemiological study of 6931 subjects (1996–2000) | Clinical attachment level $\geqslant 3$ mm was used to define periodontitis | Coronary artery calcification (Agatston score) | OR: 1.5, 95% CI: 0.5–4.2<br>Not statistically significant<br>Adjusted for demographic factors |
| Shimazaki et al. (2004) | Case–control study of 957 subjects | Periodontal status of 1,111 374 males and 583 female Japanese with $\geqslant 10$ teeth was studied. | Subjects without heart disease as defined by ECG analysis were studied | PPD definition:<br>OR: = 1.7 95% CI: 1.01–2.0<br>CAL definition<br>OR: 1.7, 95% CI: 1.1–2.7) |
| Beck et al. (2005) | Cross-sectional study and a subset of participants in the Atherosclerosis Risk in Communities (ARIC) Study | Routine clinical data<br>Subgingival samples<br>Antibody titres to a selection of bacteria including:<br>*A. actinomycetemcomitans,*<br>*C. ochracea*<br>*P. intermedia*<br>*T. denticola* | Coronary heart disease (ACS) | The study failed to identify an association between ACS and periodontitis based on clinic data. Microbiological data suggested significant odds ratios for some bacteria (see text) |

*Table 1*. (Contd.)

| Authors | Study design | Periodontal diagnosis | Medical diagnosis | Association |
|---|---|---|---|---|
| Engebretson et al. (2005) | Case–control study | Radiographic assessment of carotid calcification and alveolar bone loss | Ultrasound | OR: 3.6, 95% CI: 1.4–9.7 Association between bone loss and carotid artery plaque |
| Buhlin et al. (2005) | Case–control study Women only | Assessments were performed for: Number of remaining teeth and pathological periodontal pockets ($\geqslant$4 mm), Denture/no dentures Vertical bone loss | Subjects treated for coronary heart disease (angioplasty, by-pass grafting) | Periodontal pockets and coronary heart disease OR: 3.8, 95% CI: 1.68–8.74), Dentures and coronary heart disease: OR of 4.6 (0.99–21.28). No relationship to vertical bone loss |
| Cueto et al. (2005) | Case–control study | Percentage of sites with clinical attachment loss and probing pocket depth were dichotomized | Medically confirmed acute coronary syndrome | Adjusted OR: 3.1 |
| Holmlund et al. (2006) | Case–control study, referred dental patients for periodontal care | Periodontal index scale 0–4 dependent on extent of bone loss (defined as $>$1/3 root length, bleeding on probing and teeth with furcation | Subject self-report of a history of myocardial infarction or high blood pressure (not defined) | Periodontitis and myocardial infarction OR: 2.7, 95% CI: 1.1–6.5 |
| Spahr et al. (2006) | Case–control study | CPITN index | Angiography confirmed coronary heart disease and controls with no medical history | OR, 1.67 95% CI, 1.08–2.58 |
| Geismar et al. (2006) | Case–control study | Full mouth periodontal exam. Radiographic assessments | Routine serum assay. Confirmed medical conditions coronary disease (0110) or health ($n = 140$) | OR = 6.6 (95% CI: 1.9 to 25.6 Bone Loss |
| Rech et al. (2007) | Case–control study | Probing pocket depth $>$3 mm, and/or bleeding on probing, and/or loss of clinical attachment, and/or bone loss. Diagnosis defined by clinicians unaware of medical status | ACS consecutive cases with hospital diagnosis | OR = 4.5 95% CI: 1.3–15.6 |

ACS, acute coronary syndrome; CHD, coronary heart disease; OR, odds ratio.

Streptococcal species have also been linked to acute coronary syndrome (Li et al. 2000, Herzberg et al. 2005, Nomura et al. 2006, Plummer & Douglas 2006, Renvert et al. 2006). In oral biofilm formations, streptococci co-aggregate with Gram-negative bacteria including *Porphyromonas gingivalis* and the same mechanism may be part of colonization of *P. gingivalis* on endothelial cells (Maeda et al. 2004). Others have, however, failed to demonstrate that the counts of *Aggregatibacter actinomycetemcomitans, P. gingivalis, Parvimonas micra, Dialister pneumosintes,* or *Campylobacter rectus* could be associated with cardiovascular disease as defined by angiography (Nonnenmacher et al. 2007).

#### Sero-epidemiologic studies

A majority of medical studies suggesting an association between antibody titres against common pathogens and cardiovascular diseases including stroke have particularly focused on *C. pneumoniae, and H. pylori* (Table 3). Recent systematic reviews and meta-analysis of published reports have identified that elevated antibody titres to bacteria associated with periodontitis can be linked to cardiovascular disease risk (Meurman et al. 2003, Mustapha et al. 2007). A summary of studies on serum antibody titres to bacteria associated with periodontitis and cardiovascular disease is presented (Table 4). High antibody titers to *A. actinomycetemcomitans* specifically have been associated with coronary heart disease (Pussinen et al. 2004a, b, 2005, 2007a, b, Beck et al. 2005, Vilkuna-Rautiainen et al. 2006). Serum immunoglobulin A (IgA) and IgG antibody titres to *A. actinomycetemcomitans* have also been linked to future stroke event (Pussinen et al. 2004a).

#### Traditional cardiovascular risk factors

##### *Age*

Older patients often suffer from many diseases and many geriatric subjects with acute coronary syndrome have multi-organ failures (Taneva et al. 2004). Age is an important factor associated with both periodontitis and cardiovascular diseases. Studies in Mexico on the prevalence of periodontitis among older subjects have revealed high prevalence rates of periodontitis varying between 27% and 73%, and depending on socioeconomic and geographic conditions. Furthermore, the severity of periodontitis could be linked to high blood pressure and high body mass index (BMI) (Borges-Yáñez et al. 2006). In a study of 1763 subjects between age 38 and 88 in Japan, subclinical aortic atherosclerosis as assessed by magnetic resonance imaging (MRI) appears to be present in 50% of subjects and increasing with age (Oyama et al. 2008). In a study of people 80 years and older in an affluent part of central Stockholm, Sweden the prevalence of severe periodontitis in older adults approached 50% (Holm-Pedersen et al. 2006). Similar high prevalence rates of periodontitis in older subjects have been reported from Denmark (Krustrup & Petersen 2006). Thus

*Table 2*. Examples of studies on the role of bacteria in periodontitis as link to cardiovascular disease

| Authors | Bacteria/type of study | Study design | Condition/result |
|---|---|---|---|
| Haraszthy et al. (2000) | *A. actinomycdtemcomitas*<br>*P. gingivalis*<br>*P. intermedia*<br>*T. forsythia* | Case series with samples from 50 subjects requiring endarterectomy. PCR analysis | 61% of 36 samples positive for bacteria included one or more of the species studied. 36% were positive for *P. gingivalis* |
| Beck et al. (2005) | See also text Table 1 case–control study Beck et al | Serum antibody titres to 17 different species in periodontitis: ACS | OR: *A. actinomycetemcomitans* 1.7(95% CI: 1.2–2.7)<br>OR *C. ochracea* 2.0 (95%CI: 1.2 3.0)<br>OR: *P. nigresens* 1.7 (95% CI: 1.1–2.6) |
| Fiehn et al. (2005) | *A. actinomycetemcomitans*<br>*C. rectus*<br>*P. gingivalis,*<br>*P. intermedia, P. nigrescens*<br>*T forsythia,* and oral streptococci | 179 specimens of atherosclerotic plaque removed from carotid or femoral arteries were studied by use of PCR techniques | Viable oral bacteria could not be isolated from the atheromas.<br>DNA of periodontal pathogens was detected in atherosclerotic plaques. *P. gingivalis* was rarely found and *P. intermedia* more frequently |
| Kozarov et al. (2006) | *A. actinomycetemcomitans,*<br>*C. pneumoniae E. corrodens*<br>*P. gingivalis P. intermedia*<br>*S. aureus, S. epidermidis*<br>*S.mutans, T. forsythia*<br>*T. denticola* | 129 samples of DNA extracted from atheromas from 29 individuals were studied | DNA from oral infectious agents is commonly found in atheromas from young but especially from elderly subjects. The contribution of *C. pneumoniae* to inflammation may be minimal. *S. mutans* was found in 20%, *S. aureus* in 5% *S. epidermis* in 10%, bacteroides species were found in 17% of young and in 80% of older subjects. |
| Nomura et al. (2006) | *S. mutans* | Heart valve specimens from 52 patients and atheromatous plaque specimens from 50 patients were studied and dental plaque specimens from 41 patients before surgery | The serotype distribution in cardiovascular patients was significantly different from that in healthy subjects, suggesting that *S. mutans* serotype may be related to cardiovascular disease |
| Renvert et al. (2006) | The subgingival pathogens were assayed by the checkerboard DNA–DNA hybridization method. 40 species examined | A total of 161 consecutive surviving cases admitted with a diagnosis of acute coronary syndrome and 161 matched control subjects | The oral bacterial load of *S. intermedius, S. sanguinis, S. anginosus, T. forsythia, T. denticola*, and *P. gingivalis* are concomitant risk factors in ACS |
| Aimetti et al. (2007) | *T. forsythia, P. gingivalis,*<br>*T. denticola, P. intermedia,* and<br>*A. actinomycetemcomitans* | DNA was extracted from subgingival plaque samples and carotid atheromas from 33 subjects | Bacterial DNA was detected in 31 out of 33 endarterectomy specimens. None of the samples tested positive for DNA from periodontal pathogens |
| Gotsman et al. (2007) | *P. gingivalis* | 201 patients with stable angina or ACS who underwent a periodontal assessment. Severity of coronary artery disease was determined by the number of obstructed coronary arteries | Patients with ACS had significantly higher plaque scores, gingival index, and *P. gingivalis* counts than stable patients |
| Nakano et al. (2006) | *S. mutans* | 35 heart valves and 27 atheromatous plaques were studied by PCR | *S. mutans* was detected in 69% of heart valves and in 74% of atheromatous plaques |
| Nakano et al. (2007) | *A. actinomycetemcomitans* | 60 heart valves, 10 with endocarditis, and 50 with valvular disease and dental plaque were analysed by PCR. Serotyping of A.a. was performed | *A. actinomycetemcomitans* serotype e, and f was detected in both dental plaque and cardiovascular specimens |
| Pucar et al. (2007) | *A. actinomycetemcomitans,*<br>*C. pneumoniae*<br>*P. intermedia, P. gingivalis*<br>*T. forsythia,* and<br>Cytomegalovirus | Patients with a diagnosis of coronary artery disease were studied. Coronary arteries with atherosclerosis and 15 internal mammary arteries without clinically assessable atherosclerotic degeneration were investigated | The absence of putative pathogenic bacteria in internal mammary arteries, and their presence in a high percentage of atherosclerotic coronary arteries support the concept that periodontal organisms are associated with the development and progression of atherosclerosis |
| Zaremba et al. (2007) | *A. actinomycetemcomitans*<br>*C. rectus, F. nucleatum*<br>*P. gingivalis, P. intermedia*<br>*T .forsythia, T. denticola* | The incidence of periodontal bacteria in atherosclerotic plaque by DNA analysis from 20 subjects was studied | *A. actinomycetemcomitans* in 1/20<br>*C. rectus* in 4/20<br>*F. nucleatum* 5/20<br>*P. intermedia* in 33%<br>*P. gingivalis* in 10/20<br>*T. Denticola in 6/20*<br>*T. forsythia* in 5/20 |

ACS, acute coronary syndrome; ELISA, enzyme linked immuno sorbent assay; OR, odds ratio; PCR, polymer chain reaction; *P. intermedia*, *Porphyromonas intermedia*; *P. gingivalis*, *Porphyromonas gingivalis*; *T. forsythia*, *Tannerella forsythia*; *S. mutans*, *Streptococcus mutans*, *T. denticola*, *Tannerella denticola*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*; *C. rectus*, *Campylobacter rectus*.

it is likely that many of these older subjects also have significant severity of cardiovascular disease. There are few studies having assessed the association between periodontitis and cardiovascular disease in older subjects (Persson et al. 2002, Cueto et al. 2005). In the study by Persson et al. (2002) approximately 50% of subjects older than 60 years of age had periodontitis. In addition, approximately 55% had either a diagnosis ot atherosclerosis, or a history of

*Table 3*. The role of infection and antibody titres in subjects with cardiovascular disease in studies not assessing dental conditions (2006–2007)

| Authors | Bacteria | Antibodies studied | Disease | Results | Antibody function |
|---|---|---|---|---|---|
| Grabczewska, et al. (2006) | *C. pneumonaie* *H. pylori* | Serum IgG antibodies by ELISA | Unstable angina Case series | Antigen profile of importance, suggesting specific role of antigen profile | Not protective Diagnostic of risk |
| Kaperonis et al. (2006) | *C. pneumonia* | IgA and IgG antibodies in serum | Symptomatic and non symptomatic subjects undergoing endartherectomy | Detection of *C. pneumonia* and elevated levels of serum antibodies to *C. pneumoniae* were correlated | Not protective Diagnostic of risk |
| Pitiriga et al. (2006) | *C .pneumoniae* | IgA and IgG titres defined by immuno-fluorescence | Coronary artery disease in subjects with our without disease | Difference by IgA titres but not by IgG titres | Not protective or irrelevant Diagnostic of risk |
| Völzke et al. (2006) | *Borrelia* infection | Serum IgG antibodies to Borrelia | Cross-sectional study of carotid intima media thickness definition of atherosclerosis | Elevated IgG titres linked to artherosclerosis | Not protective and suggesting that Borrelia infection is a risk in regions with endemic lyme disease |
| Yavuz et al. (2006) | *C. pneumoniae* | IgA and IgG serum antibody titres | Atherosclerosis severity | *C. pneumoniae* seropositivity associated with dyslipidemia, and elevated IL-6 | Not protective and suggestive of *C. pneumoniae* infective etiology |
| Buyukhatipoglu et al. (2007) | *C. pneumoniae* *Cytomegalovirus (CMV)* | Serum IgG antibody titres | Atheroesclerosis in haemodialysis subjects and controls | Correlation between extent of carotid media thickening and IgG titres to *C. pneumoniae* but not to CMV | Not protective to *C. pneumoniae* and irrelevant to CMV |
| Hagiwara et al. (2007) | *C. pneumoniae* *H. pylori* *Cytomegalovirus* *Herpes simplex virus* | Serum IgA and IgG titres by ELISA | Severe carotid artery stenosis a case series of 50 Japanese subjects | None of the different antibody titres correlated with degree of stenosis | Irrelevant to CVD and periodontitis in Japanese subjects |
| Jha et al. (2007) | *C. pneumoniae* | Serum IgA and IgG antibodies by ELISA | Coronary artery disease in subjects with our without disease | Presence of *C. pneumoniae* and elevated IgA+IgG titres linked to coronary heart disease | Not protective Indicative of risk |
| Piechowski-Jóźwiak et al. (2007) | *C. pneumoniae* | Serum IgA and IgG antibodies by ELISA | Young adults with ischaemic stroke and healthy controls | Increased risk with elevated IgA titres to *C. pneumoniae* OR: 9.6 95% CI: 4.8–18.3 irrelevant to IgG | Not protective Diagnostic of risk |
| Yoshikawa et al. (2007) | *Helicobacter pylori* | Serum IgG antibodies by ELISA | Early stage of atherosclerosis in subjects with disease and in healthy controls | Increased risk in both younger and older subjects | Not protective Indicative of risk |

HSP, heat schock protein; *C. pneumoniae*, *Chlamydia pneumoniae*.

stroke, very high blood pressure, or acute coronary syndrome. In another study, an association between age and dental conditions in relation to stroke has also been presented (Lee et al. 2006).

### *Gender*

There is evidence to suggest that the extent of atheroma assessed by intravascular ultrasound in women is less severe and prevalent than in men and independent of other traditional cardiovascular risk factors (blood pressure, serum LDL levels, and BMI) (Nicholls et al. 2007). Gender-related risk factors and cardiovascular disease outcomes in relation to periodontitis remain largely unknown (Pilote et al. 2007). Data from the population-based study of health in Pomerania (SHIP) (1913 subjects), have, however, identified an association between tooth loss and left ventricular hypertrophy in women but not in men (Völzke et al. 2007). Similarly, Desvarieux et al. (2004) have reported that measures of poor oral health including tooth loss and periodontitis could be related to subclinical atherosclerosis in men but not in women. Clinical measures of periodontitis (number of probing pocket depths $\geqslant 4$ mm) have been associated with coronary heart disease but only in women after controlling for age, smoking, BMI, diabetes, education, and place of birth (Buhlin et al. 2005). Other investigators have failed to identify gender differences in the association between periodontitis and cardiovascular diseases (Andriankaja et al. 2007). Thus, the role of female gender as effect modifier in the association between periodontitis and risk for cardiovascular disease is unclear. It may, in part, depend on the fact that women might be less likely to survive a heart attack (Radovanovic et al. 2007).

### *Socioeconomic factors*

The disease burden and loss of economic output associated with chronic diseases, mainly cardiovascular diseases,

*Table 4*. The role of infection and antibody titres in subjects with periodontitis in relation to cardiovascular disease

| Authors | Bacteria | Antibodies studied | Disease | Results | Antibody function |
|---|---|---|---|---|---|
| Furuichi et al. (2003) | *A. actinomycetem-comitans*<br>*P. gingivalis* | Serum antibodies to *P. gingivalis* fimbriae, and whole cell *P. gingivalis,* and *A. actinomycetem-comitans* | Periodontitis and risk markers for cardiovascular disease (CRP, lipidemia,blood pressure, body mass index, WBC counts | Significant association between antibody titer levels and risk markers for CVD | Elevated titres suggestive of CVD risk |
| Pussinen et al. (2004b) | *A. actinomycetem-comitans*<br>*P. gingivalis* | Serum IgA and IgG to these bacteria | Case–control study of subjects with or without myocardial infarction but unknown dental status | No association for IgA or IgG titres to *A. actinomycetem-comitans* and myocardial infarction was found. No link between IgG titer but for IgA titres to *P. gingivalis* and myocardial infarction | Infection by *P. gingivalis* as assessed by serum titres may increase the risk for myocardial infarction |
| Beck et al. (2005) | *A. actinomycetem-comitans C. ochraceae*<br>*P. intermedia*<br>*T. denticola*<br>*V. parvula* | Serum IgG antibody titres to 17 oral pathogens including *P. gingivalis* | Periodontitis and coronary heart disease | See text: contradictory to previous report | Antibody titres to bacteria listed suggestive of CVD risk. *P. gingivalis* was not included |
| Johansson et al. (2005) | *A. actinomycetem-comitans* | Serum antibodies to A.a. leukotoxin | Stroke event but with no information on dental conditions | Elevated titres and reduced risk in women but elevated titres and risk for stroke in men | Conflicting impact of antibody titres by gender |
| Pussinen et al. (2005) | *A. actinomycetem-comitans P. gingivalis* | Serum IgA and serum IgG titres to bacteria listed | ACS incl. death. No information on dental conditions | *A. actinomycetem-comitans* high level IgA titres (OR: 2.0, 95% CI; 1,2–3.3)<br>*P. gingivalis* (OR: 2.1, 95% CI: 2.1–3.4) | High titres associated with risk of sub-clinical, and coronary disease |
| Vilkuna-Rautiainen et al. (2006) | Herpes simplex virus<br>*A. actinomycetem-comitans*<br>*P. gingivalis* | Serum IgA and IgG titres | Relationship between serum titres to CVD risk and markers of HDL, cholesterol | Combined HSV and *P. gingivalis* antibodies inversely correlated to HDL | Enhanced CVD risk by combined high titer levels and reduced HDL counts |
| Pussinen et al. (2007a) | *A. actinomycetem-comitans*<br>*P. gingivalis* | Serum IgA and serum IgG to bacteria listed | Case–control study on stroke. No knowledge about dental conditions | Higher stroke risk in never smoking men for elevated IgA titres. In women for IgG titres and stroke | Antibody titer differences by gender and risk for stroke |
| Yamazaki et al. (2007) | 12 different bacteria including *P. gingivalis* 381 and *P. gingivalis* SU63 | Serum IgG titres by ELISA | Case–control study subjects with coronary heart diseases, or periodontitis, or healthy subjects | A high frequency of antibody positivity for *P. gingivalis* Su63 but not for FDC381 disease subjects | Elevated antibody titres to high virulent *P. gingivalis* a risk for CVD |

Acs, acute coronarty syndrome; CVD, cardiovascular disease; HDL, high density lipoprotein; HSV, herpes simplex virus; *A. actinomycetem*, *Aggregatibacter actinomycetemcomitans*; *P. gingivalis*, *Porphyromonas gingivalis*; *T. denticola*, *Tannerella denticola*.

account for around 80% of the total burden of chronic disease mortality in developing countries (Abegunde et al. 2007). Less affluent socioeconomic conditions in childhood may have a modest persisting influence on risk of coronary heart disease later in life (Ramsay et al. 2007). Thus, age-adjusted odds of coronary heart disease were 2.2 times higher for low-income groups than for high-income groups and with no gender differences (Kivimäki et al. 2007). In a Swedish study comprising >340,000 subjects, data have suggested that socioeconomic factors affect the mortality rate of ischemic coronary disease also when adjusted for age (Chaix et al. 2007). Several studies have suggested a robust association between severe periodontitis and specific socioeconomic factors including low education, low income, and belonging to disadvantaged neighbourhoods (Borrell et al. 2006a, b, Peres et al. 2007). There are no studies that specifically have considered the relationship between socioeconomic status and periodontitis and the impact of these factors on coronary heart disease, atherosclerosis, or stroke.

### *Smoking*

Tobacco use is one of the most important causes of acute coronary syndrome globally, and especially in men (Teo et al. 2006). Data suggest that since a public smoking ban was introduced in New York city the rate of hospital admissions with a diagnosis of acute coronary syndrome decreased by 8%. This was solely accounted for by the impact of reduced smoking (Juster et al. 2007). The early work on a relationship between periodontitis and cardiovascular disease by DeStefano et al. (1993)

was criticized based on the management of the data in relation to smoking habits as a confounding factor (Hujoel et al. 2001). Thus, when adjusted for smoking Hujoel et al. (2001) failed to reach the same conclusions as DeStefano et al. (1993). Data derived from large population based case–control studies have demonstrated that the association between periodontitis and cardiovascular disease was identified independent from the possible confounding effect of smoking (Persson et al. 2005b, Holmlund et al. 2006, Andriankaja et al. 2007). Additional studies are needed to better understand the role of smoking in this potential link between periodontitis and cardiovascular diseases.

### *Metabolic factors*

BMI has been strongly linked to cardiovascular disease, and especially in relation to coexisting diabetes mellitus (Balkau et al. 2007). An association between high body weight measures early in life and an increased risk for heart disease has been reported (Lawlor & Leon 2005). Data suggest that greater body weight has an influence on blood pressure and serum cholesterol levels, and that this may account for approximately 45% of the increased risk of future coronary heart disease (Bogers et al. 2007).

Thus, the effects of increasing body weight, mostly in the western world, could outweigh any effort made to reduce cardiovascular risk by smoking cessation, or perhaps periodontal intervention. An association between a high BMI and periodontitis has been demonstrated (DallaVecchia et al. 2005, Saito et al. 2005, Linden et al. 2007). When controlling for BMI periodontal conditions in women has been linked to coronary heart disease (Buhlin et al. 2005).

LDL are involved in the transport cholesterol in the blood circulation and clearly implicated in the development and progression of atherosclerosis resulting in heart attack, stroke, and peripheral vascular diseases. HDL have been implicated in the transport of cholesterol to the liver for its excretion or re-utilization. Thus, the combination of high LDL and low HDL levels are therefore predictive of cardiovascular disease (Barter et al. 2007). Thus high LDL and low HDL would suggest a high risk of cardiovascular disease and in contrast to low serum LDL and high serum HDL levels.

Data have also suggested a relationship between elevated fasting serum triglyceride levels and measures of systemic inflammation including white blood cell (WBC) counts (Rivera et al. 2007). The relationship between hypertriglyceridemia and low-grade inflammation defined by WBC counts might also be mediated by insulin resistance (Onat et al. 2006, Shimazaki et al. 2007).

A trend of a dose dependent relationship between serum levels of metabolic markers including triglycerides, total cholesterol, LDL, HDL, and blood glucose levels have been suggested in subjects with severe periodontitis (Katz et al. 2002, Nibali et al. 2007).

### *Hypertension*

Recent evidence have linked periodontitis with high blood pressure (Inoue et al. 2005, Borges-Yáñez et al. 2006). Other measures of poor oral health (tooth loss) have been associated with hypertension (Völzke et al. 2006). Further studies are needed to confirm this relationship as many adults suffer from high blood pressure and use medication to control of blood pressure.

### *Stress*

Financial stress impacts on the individual inflammatory burden resulting in elevated serum levels of several biomarkers [interleukin-1 (IL), -6, and higher serum high sensitivity CRP] (Gèmes et al. 2007). Older subjects with a major depression disorder have higher levels of high sensitivity CRP and also present with severe coronary disease (Andrei et al. 2007). Other studies have suggested that the association between stress and elevated tissue plasminogen activator (t-PA) antigen levels may represent one plausible mechanism behind the accelerated rate of developing a prothrombotic and increased morbidity and mortality in cardiovascular diseases (Mausbach et al. 2007, Shakir et al. 2007).

Studies of older depressed subjects with elevated risk for cardiovascular disease have shown a hypocortisol response to acute stress. This impaired cortisol response might contribute to chronic inflammation reflected as elevated high-sensitivity CRP values in depressed patients and result in an increased cardiovascular disease risk (Taylor et al. 2006a). In an age adjusted model analysis based on 1400 subjects, the effects of stress associated with financial strain and distress could be linked to more severe periodontitis (Genco et al. 1999) and to poor treatment outcomes (Elter et al. 2002). Data have also suggested that subjects with periodontitis and with inadequate stress behaviour strategies (defensive coping) are at greater risk for severe periodontitis (Wimmer et al. 2002, Ng & Leung 2006). Other studies have, however, found no significant association between periodontitis and psychosocial factors in older subjects (Persson et al. 2003b, Solis et al. 2004, Castro et al. 2006). Differences in periodontitis and/or psychological status, age, and ethnicity may explain these differences in conclusions. The fact that stress has been identified both in cardiovascular disease, and in dental studies suggests that stress might be a risk factor for both conditions and that stress may trigger an inflammatory response expressed independently in cardiovascular diseases and in periodontitis. Further studies are needed to assess the impact of stress on the link between periodontitis and cardiovascular diseases.

### *Bacteremia*

One mechanism how periodontitis may be associated with cardiovascular diseases is through bacteremia. The levels of streptococci spp. in blood samples following periodontal intervention may be higher than for any other group of bacteria (Daly et al. 2001). This observation is important as streptococci might be specifically linked to a risk for cardiovascular diseases (Herzberg et al. 2005, Renvert et al. 2006). Data suggest that 80% of subjects present with positive bacterial cultures immediately following subgingival debridement (Forner et al. 2006a, b, Lafaurie et al. 2007). Others have, however, shown that the incidence of bacteremias following periodontal procedures are low (Kinane et al. 2005) or almost non-measurable (Hartzell et al. 2005). Thus, the role of bacteremia in the link between periodontitis and cardiovascular disease remains unclear.

## Blood markers of inflammation

### *IL-6 assessment*

IL-6 is a pro-inflammatory cytokine secreted by T cells and macrophages to

stimulate immune response to tissue damage leading to inflammation and a potential risk marker of future cardiovascular disease (i.e. Giannessi et al. 2007, Woodward et al. 2007). Several studies have assessed the link between periodontitis and serum IL-6 levels suggesting that subjects with untreated periodontitis have elevated serum IL-6 levels (Loos et al. 2000, Ide et al. 2004, Ioannidou et al. 2006b, Pussinen et al. 2007a). There appears to be no studies assessing the additive effect of periodontitis on IL-6 levels in subjects with diagnosed cardiovascular disease. It should, however, be recognized that the relationship between cytokine serum levels (IL-6, and TNF-α) is disputed and that several studies have not been able to associate levels of such cytokines to cardiovascular events (Sukhija et al. 2007).

Conflicting results on changes in serum IL-6 levels following periodontal therapy have also been published (improving: D'Aiuto et al. 2004; no effect: Ide et al. 2003, Yamazaki et al. 2005, Elter et al. 2006, Talbert et al. 2006). Excluding subjects with a self-reported history of cardiovascular, kidney, liver, or lung disease, it has been demonstrated that 24 h after intensive periodontal intervention the treatment resulted in an acute short-term systemic inflammatory response expressed as an increase in IL-6 levels (Tonetti et al. 2007).

### *CRP assessments*

Measuring and determining the kinetics of changes in serum of high sensitivity CRP has been proven to be useful in monitoring disease progression, or the effectiveness in the treatment of diseases that triggers a systemic inflammatory response (Mora et al. 2006, Tsimikas et al. 2006, Bansal & Ridker 2007). A summary background, and conclusions from individual studies on high sensitivity CRP values and periodontitis are presented (Table 5). A recent systematic review and meta-analysis failed to support the hypothesis that periodontal treatment can reduce systemic high sensitivity CRP levels (Ioannidou et al. 2006a).

The relationship reported between periodontitis and serum high sensitivity CRP is greatly affected by the type of individuals recruited in the comparative studies, the control of systemic disease by other means, and the definition of periodontitis (Loos et al. 2000, Ajwani et al. 2003, Craig et al. 2003, Saito et al. 2003, Deliargyris et al. 2004, Persson et al. 2005a, Havemose-Poulsen et al. 2006, Salzberg et al. 2006).

The number of remaining teeth and clinical evidence of periodontitis has been associated with an increased risk for cardiovascular disease (Beck et al. 1996, Elter et al. 2004, Geerts et al. 2004, Latronic et al. 2007), and including sudden cardiac death (Karhunen et al. 2006). The presence of *P.gingivalis, Porphyromonas intermedia, C. rectus*, and *Tannerella forsythia* in subgingival samples has also been associated with elevated high sensitivity CRP levels (Noack et al. 2001).

Results from intervention studies have suggested that within the first day of therapy serum high sensitivity CRP values may significantly increase (D'Aiuto et al. 2005a, b). Whether such sharp increases in serum high-sensitivity CRP values suggest an acute cardiovascular disease risk remains unknown. It might not be possible to reduce serum high sensitivity CRP values to levels before the periodontal intervention 6 months following therapy (Tonetti et al. 2007).

### *WBC counts*

Patients with acute coronary syndrome present with elevated WBC counts (Avramakis et al. 2007). WBC counts within normal range in subjects with periodontitis have been reported (Loos et al. 2000, Dietrich et al. 2002, Montebugnoli et al. 2005). Others have demonstrated that serum WBC counts are associated with acute coronary syndrome but also that subjects confirmed as not having cardiovascular disease but diagnosed with periodontitis present with higher serum WBC counts than periodontally healthy control subjects (Persson et al. 2003a, 2005a, Buhlin et al. 2005, Bender et al. 2006, Renvert et al. 2006). A significant decrease in WBC counts following periodontal therapy in subjects with aggressive periodontitis has been reported (Dietrich et al. 2002). Salivary matrix metalloproteinase-8 levels are associated with periodontitis among subjects who also have cardiovascular disease (Furuholm et al. 2006). Such leukocyte host immunity driven proteolytic enzymes may be part of a biological explanation to the association between periodontitis and cardiovascular diseases.

### *Endothelial cell assessments*

Plasminogen activator inhibitor-1 (PAI-1) is the principal inhibitor of tPA and urokinase (uPA), and closely associated with increased risk for the development of atherosclerosis. In inflammatory conditions in which fibrin is deposited in tissues, PAI-1 appears to play a significant role in the progression to fibrosis (Hoekstra et al. 2004). Increased PAI-1 concentrations are independent risk markers for major adverse cardiac events because of its role in fibrinolysis (Marcucci et al. 2006). PA-1 behaves also as an acute phase protein and is regulated by IL-1 and by TNF-α (Irigoyen et al. 1999). Elevated levels of PA-1 have been reported in subjects with periodontitis (Montebugnoli et al. 2005, Bizzarro et al. 2007). This may increase the potential risk for impaired fibrinolysis, a condition that may result in a prothrombotic state and a potential risk for cardiovascular disease through thrombosis.

Periodontal intervention studies of subjects with periodontitis but no medically confirmed status have demonstrated that PA-1 increase occurs shortly after therapy. Six months following non-surgical periodontal therapy with adjunct local antibiotics, no difference in PA-1 was noticed (Tonetti et al. 2007). This was not consistent with the results of another intervention trial that included a decrease in PA-1 and TPA following tooth eradication (Taylor et al. 2006a, b). In the study by Taylor et al. (2006a, b) subjects were confirmed as having one or more medically compromising medical conditions. This may explain differences in the results obtained.

A number of non-invasive subclinical markers of cardiovascular disease exist. This includes: computed tomography of the coronary arteries, ultrasound of the carotid arteries, echocardiography, MRI, ankle-brachial index, microalbuminuria, flow-mediated dilation in the brachial artery, and pulse wave form analysis are not highly correlated with each other and do not include propensity for the important atherosclerotic phase of plaque rupture, and do not fully substitute for studies of clinical cardiovascular disease endpoints (Jacobs & Crow 2007).

Endothelial dysfunction precedes clinical manifestation of atherosclerosis (Pellegrino et al. 2005). There is evidence to suggest that periodontitis may

*Table 5*. Selection of studies assessing serum (high sensitivity) C-reactive protein (C-rp) values and periodontal condition under different conditions

| Publication | Study design | Results and author conclusions | Reviewer conclusion |
|---|---|---|---|
| Iwamoto et al. (2003) | Case series: 15 subjects with chronic periodontitis receiving subgingival debridement and antibiotics | Levels of TNF-α, hs-CRP, and adiponection were studied before and 1 month after treatment including antibiotics | Effective reduction of TNF-α, hsC-RP, (C-rp from a mean of 1.7–0.9 mg/l). Large individual variation |
| Saito et al. (2003) | Case series: 179 Japanese men aged 50–54 years old, with at least 10 teeth, were examined as part of a comprehensive health examination | ABL around posterior teeth associated with elevated C-rp in Japanese men, suggesting an association between periodontal disease and increased risk of type 2 diabetes and CVD | Subjects in the highest tertile of alveolar bone loss had an increased risk for C-rp elevation > or = 1.3 mg/l (OR = 8.20; 95% CI: 1.6–40.7, $p = 0.01$) |
| Seinost et al. (2005) | Case–control study: 61 subjects of3 months duration including debridement and antibiotics in treatment group | Change in serum CRP following treatment | Healthy subjects 0.8 mg/l (SD ± 0.8). Periodontitis subjects before treatment 1.7 mg/l (SD ± 1.6) Periodontitis subjects after treatment 1.1 (SD+0.9) |
| Best et al. (2005) | Case–control study: 1131 older subjects with or without periodontitis/positive bacterial enzyme test (BANA test) and serum markers of inflammation: CRP, Il-6, TNF-α | Periodontal disease and infection may be modifiable risk indicators to elevated levels of CRP in older people | Periodontitis in the presence of periodontitis (BANA test) is linked to elevated TNF-α, and IL-6 levels in older subjects. This may specifically suggest the link between periodontitis and cardiovascular diseased susceptible subjects |
| D'Aiuto et al. (2005a, b) | Longitudinal case–control study: 24 subject in CTR, 21 subject on SC and 20 subj ect on SC+local antibiotics period: 2 months | CRP reductions significant to the control only in non-smokers | Small study groups (subgroups). Mean reduction in CRP in test groups 0.5 mg/l |
| Yamazaki et al. (2005) | Case–control+intervention study of 24 periodontitis subjects receiving non-surgical periodontal therapy | Trend toward higher CRP levels in patients at baseline compared with control subjects. Decrease after treatment was not significant | Limited effect by periodontal therapy on IL-6, TNF-α, and serum CRP levels. Periodontal therapy did not reduce CVD risk as defined by surrogate marker |
| Briggs et al. (2006) | Case–control study 92 periodontitis cases and 79 healthy controls | Median CRP in periodontitis subjects 2.1 and 1.4 mg/l in controls. Mean age was 58 years | Periodontitis and risk for coronary heart disease OR = 3 1, 95% CI: 1.0–9.2 ($p < 0.05$) C-rp (high/low): Periodontitis OR 0.1, 95% CI: 0.5–2.5 NS |
| Elter et al. (2006) | Case series; 22 systemically healthy subjects treated for chronic periodontitis. Data from before and after debridement | Change in high sensitivity CRP over 1 month was monitored | Pretreatment 3.6 mg/l (SD+9.5) Post treatment 3.3 mg/l 8 SD+5.1). Mean decrease: 0.3 mg/l |
| Franek et al. (2006) | Case–control study subject with kidney disease with (17) or without kidney disease (27) | Patients with kidney disease and severe periodontitis had mean CRP = 13.2 mg/l. Patients with kidney disease without periodontitis had CRP means 10.4 mg/l $p < 0.05$) confirmed by multiple regression analysis | The chronic kidney disease was responsible for CRP values and periodontitis contributed a minor element |
| Salzberg et al. (2006) | Case–control study Serum samples were collected from 93 patients with generalized aggressive periodontitis and from 91 healthy controls | Patients with aggressive periodontitis have statistically significant elevations in serum CRP levels compared with subjects without periodontitis | Aggressive periodontitis may induce a severe host inflammatory response that can be linked to systemic disease |
| Blum et al. (2007) | Case–control study 9+9 subjects with or without severe periodontitis | Mean hs CRP levels decreased from 2.97–2.3 mg/l ($p = 0.01$) | Small study group. Decrease in CRP on average 0.7 mg/l |
| Kshirsagar et al. (2007) | Cross-sectional study: 5537 subjects chronic hemodialysis patients with or without periodontitis | Severe periodontitis was linked to low serum albumin (OR = 8.2; 95% CI: 1.6–41.8; $p = 0.01$) but not to RP values | No observed association of severe periodontitis with CRP was found |

IS, intervention study; SD, subgingival debridement.

promote endothelial dysfunction as assessed by flow mediated dilatation of the artery (Amar et al. 2003). This has not been confirmed by brachial ankle pulse velocity assessments in subjects with periodontitis (Miyaki et al. 2006). Some studies suggest that periodontal therapy may improve brachial artery flow rate in subjects with periodontitis but with no medically confirmed diagnosis of cardiovascular disease (Mercanoglu et al. 2004, Seinost et al. 2005, Elter et al. 2006, Blum et al. 2007, Tonetti et al. 2007).

*IMT*

Cross-sectional and prospective evidence correlates IMT with cardiovascular disease. B-mode ultrasound measurement of the inner layers of the carotid wall, provides a well-validated index of

sub-clinical atheroma (Simon et al. 2002, de Groot et al. 2004). Periodontitis has also been associated with IMT (Beck et al. 2001). A relationship between periodontal microbiology and subclinical atherosclerosis assessed by IMT has been documented (Desvarieux et al. 2005). There are no studies that have assessed the impact on IMT as a result of periodontal interventions.

## Discussion

During the last two decades, there has been an increasing interest in the impact of oral health, specifically periodontitis, on cardiovascular diseases. In one meta-analysis the findings resulted in a conclusion that periodontitis and poor oral health overall indeed contribute to the pathogenesis of cardiovascular disease (Meurman et al. 2004). Furthermore, another meta-analysis identified that the level of systemic bacterial exposure from periodontitis is the biologically pertinent exposure with regard to atherosclerotic risk (Mustapha et al. 2007). This conclusion can be illustrated by the only existing study that has assessed the subgingival microbiota in subjects with acute coronary syndrome shortly after being released from the hospital. The study demonstrated that significantly higher levels of 19/40 bacterial species could be identified in subgingival samples from subjects with a recent history of acute coronary syndrome in comparison to subjects confirmed not to have cardiovascular disease (Renvert et al. 2006). Thus the role of periodontal infections as a causative factor in the link to cardiovascular disease must be further explored.

The meta-analysis by Bahekar et al. (2007) has demonstrated that having periodontitis might enhance the risk for cardiovascular disease but that this risk is not robust. Some studies have provided high ODs between periodontitis and cardiovascular diseases (i.e. Meurman et al. 2003, Persson et al. 2003a, Buhlin et al. 2005, Engebretson et al. 2005, Geismar et al. 2006, Rech et al. 2007). These studies have used alveolar bone loss as a cumulative expression of chronic periodontitis rather than a temporal expression of inflammation (i.e. bleeding on probing and probing pocket depth). Concurrently, others have shown that probing pocket depth and clinical attachment levels as diagnostic markers of periodontitis fail to identify an association between periodontitis and cardiovascular disease (Beck et al. 2005). Such findings might discourage from intervention studies attempting at reducing the extent of bleeding on probing and probing pocket depths and thereby reducing the risk of cardiovascular disease.

Thus the strength of an association between periodontitis and cardiovascular disease based on epidemiological, and cross-sectional studies varies based on data from studies of different population of subjects. Future studies assessing the association between periodontitis and cardiovascular diseases must also consider the prevalence of both disease entities. Available studies suggest that periodontitis prevalence in older subjects is high (Terpenning et al. 2001, Persson et al. 2002, Persson et al. 2003d, Holm-Pedersen et al. 2006, Krustrup & Petersen 2006). The aspect of aging as factor in the link between periodontitis and cardiovascular diseases including stroke must be considered in future studies.

Poor oral health in general has also directly been linked to cardiovascular disease (i.e. Mattila et al. 1989, Meurman et al. 2003, Karhunen et al. 2006). The finding that tooth clearance is efficacious in reducing levels of serum markers of inflammation (Taylor et al. 2006a, b, Ellis et al. 2007) must be further investigated. In fact, the findings from these two studies suggest that the old concept of tooth clearance as a means to reduce the risk or severity of inflammatory diseases should be revisited. This may further specifically relate to older people who may have poor oral health status and chronic inflammatory diseases such as rheumatoid arthritis. Other studies have, however, demonstrated that edentulousness does not change IMT and that tooth loss and long-term periodontitis are related to subclinical atherosclerosis but only in men (Desvarieux et al. 2004).

New diagnostic and monitoring methods using validated surrogate markers will open new perspectives in the assessment of periodontal treatment outcomes and independent of any relationship to other systemic diseases (i.e. Dietrich et al. 2002, Ioannidou et al. 2006b, Jacobs & Crow 2007). In the future, genetics marker may also provide useful tools to assess associations and risks between periodontitis and cardiovascular diseases (Loos et al. 2005, Hart & Atkinson 2007, Kinane et al. 2007, O'Donnell et al. 2007, Yoshie et al. 2007).

The research on serum markers of inflammation in both cardiovascular and periodontal research is extensive. The literature clearly demonstrates that elevated proinflammatory cytokines are present in both cardiovascular diseases as well as in periodontitis. It appears that Il-6, PA-1, and WBC counts are closely related to periodontitis whereas the levels of serum hs C-rp are not conclusive.

*C. pneumoniae* is perhaps one of the few bacteria that might be associated with an increased risk for cardiovascular disease. There are, however, few studies demonstrating that *C. pneumoniae* may be present in periodontal plaque samples. (Tran et al. 1997, Mäntylä et al. 2004). There are few studies having assessed the relationship between the periodontal infection and acute coronary syndrome at the time of diagnosis demonstrating that subjects with periodontitis and acute coronary syndrome have higher counts of key pathogens in periodontal pockets than found in subjects who were medically confirmed as being healthy (Renvert et al. 2006).

Stress, socioeconomic and dietary factors are approaching the level of etiological important factors both in cardiovascular disease and periodontitis. In fact, dietary factors are also about to become etiological and involved in several diseases including cardiovascular disease and periodontitis (Kaput et al. 2005).

The data on periodontal intervention and immediate increases in serum markers of inflammation may suggest that intensive periodontal therapy may result in serious adverse events (Tonetti et al. 2007). There is only one recent study that has addressed the outcome of periodontal intervention in subjects with heart disease suggesting that periodontal intervention may not induce more serious adverse events than what might be expected in the community over a 25 months period (Beck et al. 2008). Furthermore the study demonstrated that non-surgical routine periodontal therapy did not reduce the risk of serious cardiovascular events.

Given the chronic nature of both periodontitis and cardiovascular diseases, intervention at a time when already one or both disease entities are diagnosed, periodontal intervention may not reduce future cardiovascular events, or reduce symptoms of cardiovascular

disease. Preventive care may, in fact, be the most important effort in reducing the risk for cardiovascular disease by maintaining healthy oral conditions.

## Conclusions

Available data suggest that periodontitis may have overall health consequences. The term ''cardiovascular diseases'' is a broad term and efforts are needed to specifically identify which cardiovascular diseases (i.e. stroke, acute coronary syndrome, atherosclerosis) can be linked to periodontitis. Until the precise biological mechanisms how periodontitis influences cardiovascular disease are known intervention studies should be reviewed with caution.

- Multicentre properly powered studies designed to specifically assess the prevalence and distribution of periodontitis in relation to cardiovascular diseases with focus on high-risk groups are needed.
- Cross-sectional and longitudinal studies to assess the relationship between risk exposure and host driven responses in cardiovascular and periodontal disease based on well-defined criteria are needed.
- Studies to assess the impact of confounding factors in cardiovascular diseases and periodontitis are needed.

## References


Abegunde, D. O., Mathers, C. D., Adam, T., Ortegon, M. & Strong, K. (2007) The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* **370**, 1929–1938.

Aimetti, M., Romano, F. & Nessi, F. (2007) Microbiologic analysis of periodontal pockets and carotid atheromatous plaques in advanced chronic periodontitis patients. *Journal of Periodontology* **78**, 1718–1723.

Ajwani, S., Mattila, K. J., Närhi, T. O., Tilvis, R. S. & Ainamo, A. (2003) Oral health status, C-reactive protein and mortality – a 10 year follow-up study. *Gerodontology* **20**, 32–40.

Amar, S., Gokce, N., Morgan, S., Loukideli, M., Van Dyke, T. E. & Vita, J. A. (2003) Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arteriosclerosis Thrombosis and Vascular Biology* **23**, 1245–1249.

Andrei, A. M., Fraguas, R. Jr., Telles, R. M., Alves, T. C., Strunz, C. M., Nussbacher, A., Rays, J., Iosifescu, D. V. & Wajngarten, M. (2007) Major depressive disorder and inflammatory markers in elderly patients with heart failure. *Psychosomatics* **48**, 319–324.

Andriankaja, O. M., Genco, R. J., Dorn, J., Dmochowski, J., Hovey, K., Falkner, K. L. & Trevisan, M. (2007) Periodontal disease and risk of myocardial infarction: the role of gender and smoking. *European Journal of Epidemiology* **22**, 699–705.

Atar, S., Tolstrup, K., Cercek, B. & Siegel, R. J. (2007) *Chlamydia pneumoniae* antibody titers and cardiac calcifications: a cross-sectional serological-echocardiographic correlative study. *Israel Medical Association Journal* **9**, 517–520.

Avramakis, G., Papadimitraki, E., Papakonstandinou, D., Liakou, K., Zidianakis, M., Dermitzakis, A., Mikhailidis, D. P. & Ganotakis, E. S. (2007) Platelets and white blood cell subpopulations among patients with myocardial infarction and unstable angina. *Platelets* **18**, 16–23.

Bahekar, A. A., Singh, S., Saha, S., Molnar, J. & Arora, R. (2007) The prevalence and incidence of coronary heart disease is significantly increased in periodontitis: a meta-analysis. *American Heart Journal* **154**, 830–837.

Baldassarri, L., Creti, R., Arciola, C. R., Montanaro, L., Venditti, M. & Di Rosa, R. (2004) Analysis of virulence factors in cases of enterococcal endocarditis. *Clinical Microbiology and Infection* **10**, 1006–1008.

Balkau, B., Deanfield, J. E., Després, J. P., Bassand, J. P., Fox, K. A., Smith, S. C. Jr., Barter, P., Tan, C. E., Van Gaal, L., Wittchen, H. U., Massien, C. & Haffner, S. M. (2007) International Day for the Evaluation of Abdominal Obesity (IDEA): a study of waist circumference, cardiovascular disease, and diabetes mellitus in 168,000 primary care patients in 63 countries. *Circulation* **116**, 1942–1951.

Bansal, S. & Ridker, P. M. (2007) Comparison of characteristics of future myocardial infarctions in women with baseline high versus baseline low levels of high-sensitivity C-reactive protein. *American Journal of Cardiology* **99**, 1500–1503.

Barter, P., Gotto, A. M., LaRosa, J. C., Maroni, J., Szarek, M., Grundy, S. M., Kastelein, J. J., Bittner, V. & Fruchart, J. C. (2007) Treating to new targets investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *New England Journal of Medicine* **357**, 1301–1310.

Beck, J. D., Couper, D. J., Falkner, K. L., Graham, S. P., Grossi, S. G., Gunsolley, J. C., Madden, T., Maupome, G., Offenbacher, S., Stewart, D. D., Trevisan, M., Van Dyke, T. E. & Genco, R. J. (2008) The Periodontitis and Vascular Events (PAVE) pilot study: adverse events. *Journal of Periodontology* **79**, 90–96.

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

Beck, J. D., Elter, J. R., Heiss, G., Couper, D., Mauriello, S. M. & Offenbacher, S. (2001) Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. *Arteriosclerosis Thrombosis and Vascular Biology* **21**, 1816–1822.

Beck, J., Garcia, R., Heiss, G., Vokonas, P. S. & Offenbacher, S. (1996) Periodontal disease and cardiovascular disease. *Journal of Periodontology* **67**, 1123–1137.

Bender, J. S., Thang, H. & Glogauer, M. (2006) Novel rinse assay for the quantification of oral neutrophils and the monitoring of chronic periodontal disease. *Journal of Periodontal Research* **41**, 214–220.

Best, L. G., Zhang, Y., Lee, E. T., Yeh, J. L., Cowan, L., Palmieri, V., Roman, M., Devereux, R. B., Fabsitz, R. R., Tracy, R. P., Robbins, D., Davidson, M., Ahmed, A. & Howard, B. V. (2005) C-reactive protein as a predictor of cardiovascular risk in a population with a high prevalence of diabetes: the Strong Heart Study. *Circulation* **112**, 1289–1295.

Bizzarro, S., van der Velden, U., ten Heggeler, J. M., Leivadaros, E., Hoek, F. J., Gerdes, V. E., Bakker, S. J., Gans, R. O., Ten Cate, H. & Loos, B. G. (2007) Periodontitis is characterized by elevated PAI-1 activity. *Journal of Clinical Periodontology* **34**, 574–580.

Blum, A., Front, E. & Peleg, A. (2007) Periodontal care may improve systemic inflammation. *Clinical and Investigational Medicine* **30**, 114–117.

Bogers, R. P., Bemelmans, W. J., Hoogenveen, R. T., Boshuizen, H. C., Woodward, M., Knekt, P., van Dam, R. M., Hu, F. B., Visscher, T. L., Menotti, A., Thorpe, R. J. Jr., Jamrozik, K., Calling, S., Strand, B. H. & Shipley, M. J.for the BMI-CHD Collaboration Investigators. (2007) Association of overweight with increased risk of coronary heart disease partly independent of blood pressure and cholesterol levels: a meta-analysis of 21 cohort studies including more than 300 000 persons. *Archives of Internal Medicine* **167**, 1720–1728.

Borges-Yáñez, S. A., Irigoyen-Camacho, M. E. & Maupomé, G. (2006) Risk factors and prevalence of periodontitis in community-dwelling elders in Mexico. *Journal of Clinical Periodontology* **33**, 184–194.

Borrell, L. N., Beck, J. D. & Heiss, G. (2006a) Socioeconomic disadvantage and periodontal disease: the Dental Atherosclerosis Risk in Communities study. *American Journal of Public Health* **96**, 332–339.

Borrell, L. N., Burt, B. A., Warren, R. C. & Neighbors, H. W. (2006b) The role of individual and neighborhood social factors on periodontitis: the third National Health and Nutrition Examination Survey. *Journal of Periodontology* **77**, 444–453.

Briggs, J. E., McKeown, P. P., Crawford, V. L., Woodside, J. V., Stout, R. W., Evans, A. & Linden, G. J. (2006) Angiographically confirmed coronary heart disease and periodontal disease in middle-aged males. *Journal of Periodontology* **77**, 95–102.

Buhlin, K., Gustafsson, A., Ahnve, S., Janszky, I., Tabrizi, F. & Klinge, B. (2005) Oral health

in women with coronary heart disease. *Journal of Periodontology* **76**, 544–550.

Buyukhatipoglu, H., Tiryaki, O., Tahta, K. & Usalan, C. (2007) Inflammation as a risk factor for carotid intimal-medial thickening. A measure of subclinical atherosclerosis in haemodialysis patients: the role of chlamydia and cytomegalovirus infection. *Nephrology* **12**, 25–32.

Castro, G. D. C., Oppermann, R. V., Haas, A. N., Winter, R. & Alchieri, J. C. (2006) Association between psychosocial factors and periodontitis: a case–control study. *Journal of Clinical Periodontology* **33**, 109–114.

Chaix, B., Rosvall, M. & Merlo, J. (2007) Assessment of the magnitude of geographical variations and socioeconomic contextual effects on ischaemic heart disease mortality: a multilevel survival analysis of a large Swedish cohort. *Journal of Epidemiology and Community Health* **61**, 349–355.

Cohen, S. N., Friedlander, A. H., Jolly, D. A. & Date, L. (2002) Carotid calcification on panoramic radiographs: an important marker for vascular risk. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **94**, 510–514.

Craig, R. G., Yip, J. K., So, M. K., Boylan, R. J., Socransky, S. S. & Haffajee, A. D. (2003) Relationship of destructive periodontal disease to the acute-phase response. *Journal of Periodontology* **74**, 1007–1016.

Cueto, A., Mesa, F., Bravo, M. & Ocaña-Riola, R. (2005) Periodontitis as risk factor for acute myocardial infarction. A case control study of Spanish adults. *Journal of Periodontal Research* **1**, 36–42.

D'Aiuto, F., Nibali, L., Parkar, M., Suvan, J. & Tonetti, M. S. (2005a) Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. *Journal Dental Research* **84**, 269–273.

D'Aiuto, F., Parkar, M., Andreou, G., Suvan, J., Brett, P. M., Ready, D. & Tonetti, M. S. (2004) Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *Journal of Dental Research* **83**, 156–160.

D'Aiuto, F. D., Parkar, M. & Tonetti, M. T. (2005b) Periodontal therapy: a novel acute inflammatory model. *Inflammation Research* **54**, 412–414.

DallaVecchia, C. F., Susin, C., Rösing, C. K., Oppermann, R. V. & Albandar, J. M. (2005) Overweight and obesity as risk indicators for periodontitis in adults. *Journal of Periodontology* **76**, 1721–1728.

Daly, C. G., Mitchell, D. H., Highfield, J. E., Grossberg, D. E. & Stewart, D. (2001) Bacteremia due to periodontal probing: a clinical and microbiological investigation. *Journal of Periodontology* **72**, 210–214.

de Groot, E., Hovingh, G. K., Wiegman, A., Duriez, P., Smit, A. J., Fruchart, J. C. & Kastelein, J. J. (2004) Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* **109** (Suppl. 1), 33–38.

Deliargyris, E. N., Madianos, P. N., Kadoma, W., Marron, I., Smith, S. C. Jr., Beck, J. D. & Offenbacher, S. (2004) Periodontal disease in patients with acute myocardial infarction: prevalence and contribution to elevated C-reactive protein levels. *American Heart Journal* **147**, 1005–1009.

DeStefano, F., Anda, R. F., Kahn, H. S., Williamson, D. F. & Russell, C. M. (1993) Dental disease and risk of coronary heart disease and mortality. *British Medical Journal* **306**, 688–691.

Desvarieux, M., Demmer, R.T, Rundek, T., Boden-Albala, B., Jacobs, D. R. Jr., Sacco, R. L. & Papapanou, P. N. (2005) Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation* **111**, 576–582.

Desvarieux, M., Schwahn, C., Völzke, H., Demmer, R. T., Lüdemann, J., Kessler, C., Jacobs, D. R. Jr., John, U. & Kocher, T. (2004) Gender differences in the relationship between periodontal disease, tooth loss, and atherosclerosis. *Stroke* **35**, 2029–2035.

Dietrich, C. C., Hägewald, T., Kage, S. A. & Bernimoulin, J. P. (2002) White blood cell count in generalized aggressive periodontitis after non-surgical therapy. *Journal of Clinical Periodontology* **29**, 201–206.

Ellis, J. S., Averley, P. A., Preshaw, P. M., Steele, J. G., Seymour, R. A. & Thomason, J. M. (2007) Change in cardiovascular risk status after dental clearance. *British Dental Journal* **202**, 543–544.

Elter, J. L., Champagne, M. E., Offenbacher, S. & Beck, J. D. (2004) Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. *Journal of Periodontology* **75**, 782–790.

Elter, J. R., Hinderliter, A. L., Offenbacher, S., Beck, J. D., Caughey, M., Brodala, N. & Madianos, P. N. (2006) The effects of periodontal therapy on vascular endothelial function: a pilot trial. *American Heart Journal* **151**, 1–6.

Elter, J. R., White, B. A., Gaynes, B. N. & Bader, J. D. (2002) Relationship of clinical depression to periodontal treatment outcome. *Journal of Periodontology* **73**, 441–449.

Engebretson, S. P., Lamster, I. B., Elkind, M. S., Rundek, T., Sermanm, N. J., Demmer, R. T., Sacco, R. L., Papapanou, P. N. & Desvarieux, M. (2005) Radiographic measures of chronic periodontitis and carotid artery plaque. *Stroke* **36**, 561–566.

Espinola-Klein, C., Rupprecht, H. J., Blankenberg, S., Bickel, C., Kopp, H., Rippin, G., Victor, A., Hafner, G., Schlumberger, W. & Meyer, J.AtheroGene Investigators. (2002) Impact of infectious burden on extent and long-term prognosis of atherosclerosis. *Circulation* **105**, 15–21.

EUROASPIRE study group (anomynous) (1997) A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. European Action on Secondary Prevention through Intervention to Reduce Events. *European Heart Journal* **18**, 1569–1582.

Fiehn, N. E., Larsen, T., Christiansen, N., Holmstrup, P. & Schroeder, T. V. (2005) Identification of periodontal pathogens in atherosclerotic vessels. *Journal of Periodontology* **76**, 731–736.

Forner, L., Larsen, T., Kilian, M. & Holmstrup, P. (2006a) Incidence of bacteremia after chewing, tooth brushing and scaling in individuals with periodontal inflammation. *Journal of Clinical Periodontology* **33**, 401–407.

Forner, L., Nielsen, C. H., Bendtzen, K., Larsen, T. & Holmstrup, P. (2006b) Increased plasma levels of IL-6 in bacteremic periodontitis patients after scaling. *Journal of Clinical Periodontology* **33**, 724–729.

Franek, E., Blaschyk, R., Kolonko, A., Mazur-Psonka, L., Langowska Adamczyk, H., Kokot, F. & Wiecek, A. (2006) Chronic periodontitis in hemodialysis patients with chronic kidney disease is associated with elevated serum C-reactive protein concentration and greater intima-media thickness of the carotid artery. *Journal of Nephrology* **19**, 346–351.

Furuholm, J., Sorsa, T., Qvarnström, M., Janket, S. J., Tervahartiala, T., Nuutinen, P. & Meurman, J. H. (2006) Salivary matrix metalloproteinase-8 in patients with and without coronary heart disease may indicate an increased susceptibility to periodontal disease. *Journal of Periodontal Research* **41**, 486–489.

Furuichi, Y., Shimotsu, A., Ito, H., Namariyama, Y., Yotsumoto, Y., Hino, Y., Mishige, Y., Inoue, M. & Izumi, Y. (2003) Associations of periodontal status with general health conditions and serum antibody titers for *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. *Journal of Periodontology* **74**, 1491–1497.

Geerts, S. O., Legrand, V., Charpentier, J., Albert, A. & Rompen, E. H. (2004) Further evidence of the association between periodontal conditions and coronary artery disease. *Journal of Periodontology* **75**, 1274–1280.

Geismar, K., Stoltze, K., Sigurd, B., Gyntelberg, F. & Holmstrup, P. (2006) Periodontal disease and coronary heart disease. *Journal of Periodontology* **77**, 1547–1554.

Gémes, K., Ahnve, S. & Janszky, I. (2008) Inflammation a possible link between economical stress and coronary heart disease. *European Journal of Epidemiology* **23**, 95–103.

Genco, R. J., Ho, A. W., Grossi, S. G., Dunford, R. G. & Tedesco, L. A. (1999) Relationship of stress, distress and inadequate coping behaviors to periodontal disease. *Journal of Periodontology* **70**, 711–723.

Giannessi, D., Colotti, C., Maltinti, M., Del Ry, S., Prontera, C., Turchi, S., Labbate, A. & Neglia, D. (2007) Circulating heat shock proteins and inflammatory markers in patients with idiopathic left ventricular dysfunction: their relationships with myocardial and microvascular impairment. *Cell Stress Chaperones* **12**, 265–274.

Golden, S. H., Selvin, E. & Cunningham, K. E. (2007) Glycaemic status and cardiovascular disease in type 2 diabetes mellitus: re-visiting

glycated haemoglobin targets for cardiovascular disease prevention. *Diabetes Obesity and Metabolism* **9**, 792–798.

Gotsman, I., Lotan, C., Soskolne, W. A., Rassovsky, S., Pugatsch, T., Lapidus, L., Novikov, Y., Masrawa, S. & Stabholz, A. (2007) Periodontal destruction is associated with coronary artery disease and periodontal infection with acute coronary syndrome. *Journal of Periodontology* **78**, 849–858.

Grabczewska, Z., Nartowicz, E., Kubica, J. & Roœć, D. (2006) Endothelial function parameters in patients with unstable angina and infection with *Helicobacter pylori* and *Chlamydia pneumoniae*. *European Journal of Internal Medicine* **17**, 339–342.

Grau, A. J., Becher, H., Ziegler, C. M., Lichy, C., Buggle, F., Kaiser, C., Lutz, R., Bültmann, S., Preusch, M. & Dörfer, C. E. (2004) Periodontal disease as a risk factor for ischemic stroke. *Stroke* **35**, 496–501.

Hagiwara, N., Toyoda, K., Inoue, T., Shimada, H., Ibayashi, S., Iida, M. & Okada, Y. (2007) Lack of association between infectious burden and carotid atherosclerosis in Japanese patients. *Journal of Stroke and Cerebrovascular Disease* **16**, 145–152.

Haraszthy, V. I., Zambon, J. J., Trevisan, M., Zed, M. & Genco, R. J. (2000) Identification of periodontal pathogens in atheromatous plaques. *Journal of Periodontology* **71**, 1554–1560.

Hart, T. C. & Atkinson, J. C. (2007) Mendelian forms of periodontitis. *Periodontology 2000* **45**, 95–112.

Hartzell, J. D., Torres, D., Kim, P. & Wortmann, G. (2005) Incidence of bacteremia after routine tooth brushing. *American Journal of Medical Sciences* **329**, 178–180.

Havemose-Poulsen, A., Westergaard, J., Stoltze, K., Skjødt, H., Danneskiold-Samsøe, B., Locht, H., Bendtzen, K. & Holmstrup, P. (2006) Periodontal and hematological characteristics associated with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. *Journal of Periodontology* **77**, 280–288.

Herzberg, M. C., Nobbs, A., Tao, L., Kilic, A., Beckman, E., Khammanivong, A. & Zhang, Y. (2005) Oral streptococci and cardiovascular disease: searching for the platelet aggregation-associated protein gene and mechanisms of *Streptococcus sanguis*-induced thrombosis. *Journal of Periodontology* **76** (Suppl.), 2101–2105.

Hoekstra, T., Geleijnse, J. M., Schouten, E. G. & Kluft, C. (2004) Plasminogen activator inhibitor-type 1: its plasma determinants and relation with cardiovascular risk. *Thrombosis and Haemostasis* **91**, 861–872.

Holmlund, A., Holm, G. & Lind, L. (2006) Severity of periodontal disease and number of remaining teeth are related to the prevalence of myocardial infarction and hypertension in a study based on 4,254 subjects. *Journal of Periodontology* **77**, 1173–1178.

Holm-Pedersen, P., Russell, S. L., Avlund, K., Viitanen, M., Winblad, B. & Katz, R. V. (2006) Periodontal disease in the oldest-old living in Kungsholmen, Sweden: findings from the KEOHS project. *Journal of Clinical Periodontology* **33**, 376–384.

Honda, T., Oda, T., Yoshie, H. & Yamazaki, K. (2005) Effects of *Porphyromonas gingivalis* antigens and proinflammatory cytokines on human coronary artery endothelial cells. *Oral Microbiology and Immunology* **20**, 82–88.

Hujoel, P. P., Drangsholt, M., Spiekerman, C. & DeRouen, T. A. (2001) Periodontal disease and coronary heart disease risk. *Journal of American Medical Association* **284**, 1406–1410.

Ide, M., Jagdev, D., Coward, P. Y., Crook, M., Barclay, G. R. & Wilson, R. F. (2004) The short-term effects of treatment of chronic periodontitis on circulating levels of endotoxin, C-reactive protein, tumor necrosis factor-alpha, and interleukin-6. *Journal of Periodontology* **75**, 420–428.

Ide, M., McPartlin, D., Coward, P. Y., Crook, M., Lumb, P. & Wilson, R. F. (2003) Effect of treatment of chronic periodontitis on levels of serum markers of acute-phase inflammatory and vascular responses. *Journal of Clinical Periodontology* **30**, 334–340.

Inoue, K., Kobayashi, Y., Hanamura, H. & Toyokawa, S. (2005) Association of periodontitis with increased white blood cell count and blood pressure. *Blood Pressure* **14**, 53–58.

Ioannidou, E., Kao, D., Chang, N., Burleson, J. & Dongari-Bagtzoglou, A. (2006b) Elevated serum interleukin-6 (IL-6) in solid-organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium. *Journal of Periodontology* **77**, 1871–1878.

Ioannidou, E., Malekzadeh, T. & Dongari-Bagtzoglou, A. (2006a) Effect of periodontal treatment on serum C-reactive protein levels: a systematic review and meta-analysis. *Journal of Periodontology* **77**, 1635–1642.

Irigoyen, J. P., Muñoz-Cánoves, P., Montero, L., Koziczak, M. & Nagamine, Y. (1999) The plasminogen activator system: biology and regulation. *Cellular and Molecular Life Science* **56**, 104–132.

Iwamoto, Y., Nishimura, F., Soga, Y., Takeuchi, K., Kurihara, M., Takashiba, S. & Murayama, Y. (2003) Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. *Journal of Periodontology* **74**, 1231–1236.

Jacobs, D. R. Jr. & Crow, R. S. (2007) Subclinical cardiovascular disease markers applicable to studies of oral health: multiethnic study of atherosclerosis. *Annals of New York Academy of Science* **1098**, 269–287.

Janket, S. J., Jones, J. A., Meurman, J. H., Baird, A. E. & Van Dyke, T. E. (2007) Oral infection, hyperglycemia, and endothelial dysfunction. *Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics* **105**, 173–179.

Jha, H. C., Vardhan, H., Gupta, R., Varma, R., Prasad, J. & Mittal, A. (2007) Higher incidence of persistent chronic infection of *Chlamydia pneumoniae* among coronary artery disease patients in India is a cause of concern. *Biomedical Central Infectous Diseases* **30**, 48.

Johansson, A., Johansson, I., Eriksson, M., Ahrén, A. M., Hallmans, G. & Stegmayr, B. (2005) Systemic antibodies to the leukotoxin of the oral pathogen *Actinobacillus actinomycetemcomitans* correlate negatively with stroke in women. *Cerebrovascular Disease* **20**, 226–232.

Juster, H. R., Loomis, B. R., Hinman, T. M., Farrelly, M. C., Hyland, A., Bauer, U. E. & Birkhead, G. S. (2007) Declines in hospital admissions for acute myocardial infarction in New York state after implementation of a comprehensive smoking ban. *American Journal of Public Health* **97**, 2035–2039.

Kaperonis, E. A., Liapis, C. D., Kakisis, J. D., Perrea, D., Kostakis, A. G. & Karayannakos, P. E. (2006) The association of carotid plaque inflammation and *Chlamydia pneumoniae* infection with cerebrovascular symptomatology. *Journal of Vascular Surgery* **44**, 1198–1204.

Kaput, J., Ordovas, J. M., Ferguson, L., van Ommen, B., Rodriguez, R. L., Allen, L., Ames, B. N., Dawson, K., German, B., Krauss, R., Malyj, W., Archer, M. C., Barnes, S., Bartholomew, A., Birk, R., van Bladeren, P., Bradford, K. J., Brown, K. H., Caetano, R., Castle, D., Chadwick, R., Clarke, S., Clément, K., Cooney, C. A., Corella, D., Manica da Cruz, I. B., Daniel, H., Duster, T., Ebbesson, S. O., Elliott, R., Fairweather-Tait, S., Felton, J., Fenech, M., Finley, J. W., Fogg-Johnson, N., Gill-Garrison, R., Gibney, M. J., Gillies, P. J., Gustafsson, J. A., Hartman, Iv. J. L., He, L., Hwang, J. K., Jais, J. P., Jang, Y., Joost, H., Junien, C., Kanter, M., Kibbe, W. A., Koletzko, B., Korf, B. R., Kornman, K., Krempin, D. W., Langin, D., Lauren, D. R., Ho Lee, J., Leveille, G. A., Lin, S. J., Mathers, J., Mayne, M., McNabb, W., Milner, J. A., Morgan, P., Muller, M., Nikolsky, Y., van der Ouderaa, F., Park, T., Pensel, N., Perez-Jimenez, F., Poutanen, K., Roberts, M., Saris, W. H., Schuster, G., Shelling, A. N., Simopoulos, A. P., Southon, S., Tai, E. S., Towne, B., Trayhurn, P., Uauy, R., Visek, W. J., Warden, C., Weiss, R., Wiencke, J., Winkler, J., Wolff, G. L., Zhao-Wilson, X. & Zucker, J. D. (2005) The case for strategic international alliances to harness nutritional genomics for public and personal health. *British Journal of Nutrition* **94**, 623–632.

Karchmer, A. W. (1997) Infective endocarditis. In: Braunwald, E. (ed). *Heart Disease. A Textbook of Cardiovascular Medicine*, 5th edition, pp. 1077–1099. Philadelphia, USA: W.B. Saunders CO.

Karhunen, V., Forss, H., Goebeler, S., Huhtala, H., Ilveskoski, E., Kajander, O., Mikkelsson, J., Penttilä, A, Perola, M., Ranta, H., Meurman, J. H. & Karhunen, P. J. (2006) Radiographic assessment of dental health in middle-aged men following sudden cardiac death. *Journal of Dental Research* **85**, 89–93.

Katz, J., Flugelman, M. Y., Goldberg, A. & Heft, M. (2002) Association between periodontal pockets and elevated cholesterol and low density lipoprotein cholesterol levels. *Journal of Periodontology* **73**, 494–500.

Kinane, D. F., Demuth, D. R., Gorr, S. U., Hajishengallis, G. N. & Martin, M. H. (2007) Human variability in innate immunity. *Periodontology 2000* **45**, 14–34.

Kinane, D. F., Riggio, M. P., Walker, K. F., MacKenzie, D. & Shearer, B. (2005) Bacteraemia following periodontal procedures. *Journal of Clinical Periodontoogy* **32**, 708–713.

Kivimäki, M., Lawlor, D. A., Davey Smith, G., Kouvonen, A., Virtanen, M., Elovainio, M. & Vahtera, J. (2007) Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study. *American Journal of Public Health* **97**, 874–879.

Kozarov, E., Sweier, D., Shelburne, C., Progulske-Fox, A. & Lopatin, D. (2006) Detection of bacterial DNA in atheromatous plaques by quantitative PCR. *Microbes and Infection* **8**, 687–693.

Krustrup, U. & Petersen, E. (2006) Periodontal conditions in 35-44 and 65-74-year-old adults in Denmark. *Acta Odontologica Scandinavia* **64**, 65–73.

Kshirsagar, A. V., Offenbacher, S., Moss, K. L., Barros, S. P. & Beck, J. D. (2007) Antibodies to periodontal organisms are associated with decreased kidney function. The dental atherosclerosis risk in communities study. *Blood Purification* **25**, 125–132.

Kuller, L. H. (2006) Nutrition lipids and cardiovascular disease. *Nutrition Reviews* **64**, 15–26.

Kumagai, M., Yamagishi, T., Fukui, N. & Chiba, M. (2007) Carotid artery calcification seen on panoramic dental radiographs in the Asian population in Japan. *Dentomaxillofacial Radiology* **36**, 92–96.

Lafaurie, G. I., Mayorga-Fayad, I., Torres, M. F., Castillo, D. M., Aya, M. R., Barón, A. & Hurtado, P. A. (2007) Periodontopathic microorganisms in peripheric blood after scaling and root planing. *Journal of Clinical Periodontology* **34**, 873–879.

Latronic, M., Segantini, A., Cabvalini, F., Mascolo, A., Garbarino, F., Bondanza, S., debbia, E. A. & Blasi, G. (2007) Periodontal disease and coronary heart disease: an epidemiological and microbiological study. *New Microbiology* **30**, 221–228.

Lawlor, D. & Leon, D. A. (2005) Association of body mass index and obesity measured in early childhood with risk of coronary heart disease and stroke in middle age. Findings from the Aberdeeen children of the 1950s prospective cohort study. *Circulation* **111**, 1891–1896.

Lee, H. J., Garcia, R. I., Janket, S. J., Jones, J. A., Mascarenhas, A. K., Scott, T. E. & Nunn, M. E. (2006) The association between cumulative periodontal disease and stroke history in older adults. *Journal of Periodontology* **77**, 1744–1754.

Lessem, J., Driosko, C., Greenwall, H., Persson, G. R., Newman, H., Smart, G., Hopkins, L., Pacarameshwar, J., Fishbein, D., Partridge, C., Bhat, G. & Goldstein, J. (2002) Are cardiac transplant patients more likely to have periodontiitis? A case record study. *International Journal of Periodontology* **4**, 95–100.

Li, X., Kolltveit, K. M., Tronstad, L. & Olsen, I. (2000) Systemic diseases caused by oral infection. *Clinical Microbiology Reviews* **13**, 547–558.

Linden, G., Patterson, C., Evans, A. & Kee, F. (2007) Obesity and periodontitis in 60–70 year-old men. *Journal of Clinical Periodontology* **34**, 461–466.

Liu, R., Moroi, M., Yamamoto, M., Kubota, T., Ono, T., Funatsu, A., Komatsu, H., Tsuji, T., Hara, H., Hara, H., Nakamura, M., Hirai, H. & Yamaguchi, T. (2006) Presence and severity of *Chlamydia pneumoniae* and Cytomegalovirus infection in coronary plaques are associated with acute coronary syndromes. *International Heart Journal* **47**, 511–519.

Loos, B. G., Craandijk, J., Hoek, F. J., Wertheim-van Dillen, P. M. & van der Velden, U. (2000) Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. *Journal of Periodontology* **71**, 1528–1534.

Loos, B. G., John, R. P. & Laine, M. L. (2005) Identification of genetic risk factors for periodontitis and possible mechanisms of action. *Journal of Clinical Periodontology* **32** (Suppl. 6), 159–179.

Maeda, K., Nagata, H., Nonaka, A., Kataoka, K., Tanaka, M. & Shizukuishi, S. (2004) Oral streptococcal glyceraldehyde-3-phosphate dehydrogenase mediates interaction with *Porphyromonas gingivalis* fimbriae. *Microbes and Infection* **6**, 1163–1670.

Mäntylä, P., Stenman, M., Paldanius, M., Saikku, P., Sorsa, T. & Meurman, J. H. (2004) *Chlamydia pneumoniae* together with collagenase-2 (MMP-8) in periodontal lesions. *Oral Disease* **10**, 32–35.

Marcucci, R., Brogi, D., Sofi, F., Giglioli, C., Valente, S., Liotta, A. A., Lenti, M., Gori, A. M., Prisco, D., Abbate, R. & Gensini, G. F. (2006) PAI-1 and homocysteine, but not lipoprotein (a) and thrombophilic polymorphisms, are independently associated with the occurrence of major adverse cardiac events after successful coronary stenting. *Heart* **92**, 377–381.

Mattila, K. J., Nieminen, M. S., Valtonen, V. V., Rasi, V. P., Kesäniemi, Y. A., Syrjälä, S. L., Jungell, P. S., Isoluoma, M., Hietaniemi, K. & Jokinen, M. J. (1989) Association between dental health and acute myocardial infarction. *British Medical Journal* **298**, 779–781.

Mausbach, B. T., von Känel, R., Aschbacher, K., Roepke, S. K., Dimsdale, J. E., Ziegler, M. G., Mills, P. J., Patterson, T. L., Ancoli-Israel, S. & Grant, I. (2007) Spousal caregivers of patients with Alzheimer's disease show longitudinal increases in plasma level of tissue-type plasminogen activator antigen. *Psychosomatic Medicine* **69**, 816–822.

Mercanoglu, F., Oflaz, H., Öz, O., Gökbuget, A. Y., Genchellac, H., Sezer, M., Niganci, Y. & Umman, S. (2004) Endothelial dysfunction in patients with chronic periodontitis and its improvement after initial periodontal therapy. *Journal of Periodontology* **75**, 1694–1700.

Meurman, J. H., Janket, S. J., Qvarnström, M. & Nuutinen, P. (2003) Dental infections and serum inflammatory markers in patients with and without severe heart disease. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics* **96**, 695–700.

Meurman, J. H., Sanz, M. & Janket, S. J. (2004) Oral health, atherosclerosis, and cardiovascular disease. *Critical Reviews Oral Biology and Medicine* **15**, 403–413.

Miyaki, K., Masaki, K., Naito, M., Naito, T., Hoshi, K., Hara, A., Tohyama, S. & Nakayama, T. (2006) Periodontal disease and atherosclerosis from the viewpoint of the relationship between community periodontal index of treatment needs and brachial-ankle pulse wave velocity. *Biomedical Central Public Health* **14**, 131.

Miyazaki, M., Babazono, A., Kadowaki, K., Kato, M., Takata, T. & Une, H. (2006) Is *Helicobacter pylori* infection a risk factor for acute coronary syndromes? *Journal of Infection* **52**, 86–91.

Montebugnoli, L., Servidio, D., Miaton, R. A., Prati, C., Tricoci, P., Melloni, C. & Melandri, G. (2005) Periodontal health improves systemic inflammatory and haemostatic status in subjects with coronary heart disease. *Journal of Clinical Periodontology* **32**, 188–192.

Mora, S., Rifai, N., Buring, J. E. & Ridker, P. M. (2006) Additive value of immunoassay-measured fibrinogen and high-sensitivity C-reactive protein levels for predicting incident cardiovascular events. *Circulation* **114**, 381–387.

Morrison, H. I., Ellison, L. F. & Taylor, G. W. (1999) Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *Journal of Cardiovascular Risk* **6**, 7–11.

Mustapha, I. Z., Debrey, S., Oladubu, M. & Ugarte, R. (2007) Cardiovascular disease markers of systemic bacterial exposure in periodontal disease and risk: a systematic review and meta-analysis. *Journal of Periodontology* **78**, 2289–2302.

Nakano, K., Inaba, H., Nomura, R., Nemoto, H., Takeda, M., Yoshioka, H., Matsue, H., Takahashi, T., Taniguchi, K., Amano, A. & Ooshima, T. (2006) Detection of cariogenic *Streptococcus mutans* in extirpated heart valve and atheromatous plaque specimens. *Journal of Clinical Microbiolology* **44**, 3313–3317.

Nakano, K., Inaba, H., Nomura, R., Nemoto, H., Tamura, K., Miyamoto, E., Yoshioka, H., Taniguchi, K., Amano, A. & Ooshima, T. (2007) Detection and serotype distribution of *Actinobacillus actinomycetemcomitans* in cardiovascular specimens from Japanese patients. *Oral Microbiology and Immunology* **22**, 136–139.

Nakib, S. A., Pankow, J. S., Beck, J. D., Offenbacher, S., Evans, G. W., Desvarierux,

M. & Folsom, A. R. (2004) Periodontitis and coronary artery calcification: the Atherosclerosis risk in Communities (ARIC) study. *Journal of Periodontology* **75**, 505–510.

Ng, S. K. & Keung Leung, W. (2006) A community study on the relationship between stress coping affective dispositions and periodontal attachment loss. *Community Dentistry and Oral Epidemiology* **34**, 252–256.

Nibali, L., D'Aiuto, F., Griffiths, G., Patel, K., Suvan, J. & Tonetti, M. S. (2007) Severe periodontitis is associated with systemic inflammation and a dysmetabolic status: a case–control study. *Journal of Clinical Periodontology* **34**, 931–937.

Nicholls, S. J., Wolski, K., Sipahi, I., Schoenhagen, P., Crowe, T., Kapadia, S. R., Hazen, S. L., Tuzcu, E. M. & Nissen, S. E. (2007) Rate of progression of coronary atherosclerotic plaque in women. *Journal of American College of Cardiology* **49**, 1546–1551.

Noack, B., Genco, R. J., Trevisan, M., Grossi, S., Zambon, J. J. & De Nardin, E. (2001) Periodontal infections contribute to elevated systemic C-reactive protein level. *Journal of Periodontology* **72**, 1221–1227.

Nomura, R., Nakano, K., Nemoto, H., Fujita, K., Inagaki, S., Takahashi, T., Taniguchi, K., Takeda, M., Yoshioka, H., Amano, A. & Ooshima, T. (2006) Isolation and characterization of *Streptococcus mutans* in heart valve and dental plaque specimens from a patient with infective endocarditis. *Journal of Medical Microbiology* **55**, 1135–1140.

Nonnenmacher, C., Stelzel, M., Susin, C., Sattler, A. M., Schaefer, J. R., Maisch, B., Mutters, R. & Flores-de-Jacoby, L. (2007) Periodontal microbiota in patients with coronary artery disease measured by real-time polymerase chain reaction: a case–control study. *Journal of Periodontology* **78**, 1724–1730.

Nyström-Rosander, C., Edvinsson, M., Thelin, S., Hjelm, E. & Friman, G. (2006) *Chlamydophila pneumonia*: specific mRNA in aorta ascendens in patients undergoing coronary artery by-pass grafting. *Scandinavian Journal of Infectious diseases* **38**, 758–763.

O'Donnell, C. J., Cupples, L. A., D'Agostino, R. B., Fox, C. S., Hoffmann, U., Hwang, S. J., Ingellson, E., Liu, C., Murabito, J. M., Polak, J. F., Wolf, P. A. & Demissie, S. (2007) Genome-wide association study for subclinical atherosclerosis in major arterial territories in the NHLBI's Framingham Heart Study. *Biomedical central Medical Genetics* **19** (8 Suppl. 1), S4.

Onat, A., Sari, I., Yazici, M., Can, G., Hergenc, G. & Avci, G. C. (2006) Plasma triglycerides, an independent predictor of cardiovascular disease in men: a prospective study based on a population with prevalent metabolic syndrome. *International Journal of Cardiology* **108**, 89–95.

Oyama, N., Gona, P., Salton, C. J., Chuang, M. L., Jhaveri, R. R., Blease, S. J., Manning, A. R., Lahiri, M., Botnar, R. M., Levy, D., Larson, M. G., O'Donnell, C. J. & Manning, W. J. (2008) Differential impact of age, sex, and hypertension on aortic atherosclerosis. The Framingham Heart Study. *Arteriosclerosis Thrombosis and Vascular Biology* **28**, 155–159.

Paster, B. J., Olsen, I., Aas, J. A. & Dewhirst, F. E. (2006) The breadth of bacterial diversity in the human periodontal pocket and other oral sites. *Periodontology 2000* **42**, 80–87.

Pellegrino, T., Storto, G., Filardi, P. P., Sorrentino, A. R., Silvestro, A., Petretta, M., Brevetti, G., Chiariello, M., Salvatore, M. & Cuocolo, A. (2005) Relationship between brachial artery flow-mediated dilation and coronary flow reserve in patients with peripheral artery disease. *Journal of Nuclear Medicine* **46**, 1997–2002.

Peres, M. A., Antunes, J. L., Boing, A. F., Peres, K. G. & Bastos, J. L. (2007) Skin colour is associated with periodontal disease in Brazilian adults: a population-based oral health survey. *Journal of Clinical Periodontology* **34**, 196–201.

Persson, G. R., Ohlsson, O., Pettersson, T. & Renvert, S. (2003a) Chronic periodontitis, a significant relationship with acute myocardial infarction. *European Heart Journal* **24**, 2108–2115.

Persson, G. R., Persson, R. E., MacEntee, C. I., Wyatt, C. C., Hollender, L. G. & Kiyak, H. A. (2003b) Periodontitis and perceived risk for periodontitis in elders with evidence of depression. *Journal of Clinical Periodontology* **30**, 691–696.

Persson, G. R., Persson, R. E., MacEntee, M. I., Wyatt, C. C., Hollender, L. G. & Kiyak, H. A. (2003c) Periodontitis and perceived risk for periodontitis in elders with evidence of depression. *Journal of Clinical Periodontology* **30**, 691–696.

Persson, G. R., Pettersson, T., Ohlsson, O. & Renvert, S. (2005a) High-sensitivity serum C-reactive protein levels in subjects with or without myocardial infarction or periodontitis. *Journal of Clinical Periodontology* **32**, 219–224.

Persson, R. E., Hollender, L. G., MacEntee, M. I., Wyatt, C. C., Kiyak, H. A. & Persson, G. R. (2003d) Assessment of periodontal conditions and systemic disease in older subjects. *Journal of Clinical Periodontology 2003* **30**, 207–213.

Persson, R. E., Hollender, L. G., Powell, V. L., MacEntee, M., Wyatt, C.C, Kiyak, H. A. & Persson, G. R. (2002) Assessment of periodontal conditions and systemic disease in older subjects. II. Focus on cardiovascular diseases. *Journal of Clinical Periodontology* **29**, 803–810.

Persson, R. E., Kiyak, A. H., Wyatt, C. C., Macentee, M. & Persson, G. R. (2005b) Smoking, a weak predictor of periodontitis in older adults. *Journal of Clinical Periodontology* **32**, 512–527.

Piechowski-JóŹwiak, B., Mickielewicz, A., Gaciong, Z., Berent, H. & Kwieciński, H. (2007) Elevated levels of anti-*Chlamydia pneumonia*e IgA and IgG antibodies in young adults with ischemic stroke. *Acta Neurologica Scandinavica* **116**, 144–149.

Pilote, L., Dasgupta, K., Guru, V., Humphries, K. H., McGrath, J., Norris, C., Rabi, D., Tremblay, J., Alamian, A., Barnett, T., Cox, J., Ghali, W. A., Grace, S., Hamet, P., Ho, T., Kirkland, S., Lambert, M., Libersan, D., O'Loughlin, J., Paradis, G., Petrovich, M. & Tagalakis, V. (2007) A comprehensive view of sex-specific issues related to cardiovascular disease. *Canadian Medical Association Journal* **176**, 1–44.

Pitiriga, V., Lekakis, J., Kotsis, V., Protogerou, A., Ikonomidis, I., Gennimata, V. & Zakopoulos, N. (2006) Arterial stiffness and Chlamydia pneumoniae infection in coronary artery disease. Is there a link? *Scandinavian Cardiovascular Journal* **40**, 285–290.

Plummer, C. & Douglas, C. W. (2006) Relationship between the ability of oral streptococci to interact with platelet glycoprotein Ibalpha and with the salivary low-molecular-weight mucin, MG2. *FEMS Immunology and Medical Microbiolology* **48**, 390–399.

Presterl, E., Grisold, A. J., Reichmann, S., Hirschl, A. M., Georgopoulos, A. & Graninger, W. (2005) Viridans streptococci in endocarditis and neutropenic sepsis: biofilm formation and effects of antibiotics. *Journal of Antimicrobial Chemotherapy* **55**, 45–50.

Pucar, A., Milasin, J., Lekovic, V., Vukadinovic, M., Ristic, M., Putnik, S. & Kenney, E. (2007) Correlation between atherosclerosis and periodontal putative pathogenic bacterial infections in coronary and internal mammary arteries. *Journal of Periodontology* **78**, 677–682.

Pussinen, P. I., Alfthan, G., Rissanen, H., Reunanen, A., Asikainen, S. & Knekt, P. (2004a) Antibodies to periodontal pathogens and stroke risk. *Stroke* **35**, 2020–2023.

Pussinen, P. J., Alfthan, G., Tuomilehto, J., Asikainen, S. & Jousilahti, P. (2004b) High serum antibody levels to *Porphyromonas gingivalis* predict myocardial infarction. *European Journal of Cardiovascular Prevention and Rehabilitation* **11**, 408–411.

Pussinen, P. J., Nyyssönen, K., Alfthan, G., Salonen, R., Laukkanen, J. A. & Salonen, J. T. (2005) Serum antibody levels to *Actinobacillus actinomycetemcomitans* predict the risk for coronary heart disease. *Arteriosclerosis Thrombosis and Vascular Biology* **25**, 833–838.

Pussinen, P. J., Alfthan, G., Jousilahti, P., Paju, S. & Tuomilehto, J. (2007a) Systemic exposure to *Porphyromonas gingivalis* predicts incident stroke. *Atherosclerosis* **193**, 222–228.

Pussinen, P. J., Tuomisto, K., Jousilahti, P., Havulinna, A. S., Sundvall, J. & Salomaa, V. (2007b) Endotoxemia, immune response to periodontal pathogens, and systemic inflammation associate with incident cardiovascular disease events. *Arteriosclerosis Thrombosis and Vascular Biology* **27**, 1433–1439.

Radovanovic, D., Erne, P., Urban, P., Bertel, O., Rickli, H. & Gaspoz, J. M.AMIS Plus Investigators. (2007) Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. *Heart* **93**, 1369–1375.

Ramsay, S. E., Whincup, P. H., Morris, R. W., Lennon, L. T. & Wannamethee, S. G. (2007) Are childhood socio-economic circumstances related to coronary heart disease risk? Findings from a population-based study of older men. *International Journal of Epidemiology* **36**, 560–566.

Ravon, N. A., Hollender, L. G., McDonald, V. & Persson, G. R. (2003) Signs of carotid calcification from dental panoramic radiographs are in agreement with Doppler sonography results. *Journal of Clinical Periodontology* **30**, 1084–1090.

Rech, R. L., Nurkin, N., da Cruz, I., Sostizzo, F., Baião, C., Perrone, J. A., Wainstein, R., Pretto, D., Manenti, E. R. & Bodanese, L. C. (2007) Association between periodontal disease and acute coronary syndrome. *Arquivos Brasileiros de Cardiologia* **88**, 185–190.

Renvert, S., Pettersson, T., Ohlsson, O. & Persson, G. R. (2006) Bacterial profile and burden of periodontal infection in subjects with a diagnosis of acute coronary syndrome. *Journal of Periodontology* **77**, 1110–1119.

Rivera, J. J., Nasir, K., Campbell, C., Carvalho, J. A., Blumenthal, R. S. & Santos, R. D. (2007) Relation of plasma lipoprotein levels with low-grade inflammation in white men without clinical evidence of myocardial ischemia. *American Journal of Cardiology* **100**, 450–454.

Rosamond, W., Flegal, K., Friday, G., Furie, K., Go, A., Greenlund, K., Haase, N., Ho, M., Howard, V., Kissela, B., Kittner, S., Lloyd-Jones, D., McDermott, M., Meigs, J., Moy, C., Nichol, G., O'Donnell, C. J., Roger, V., Rumsfeld, J., Sorlie, P., Steinberger, J., Thom, T., Wasserthiel-Smoller, S. & Hong, Y.American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (2007) Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* **115**, 69–171.

Ross, R. (1997) The pathogenesis of atherosclerosis. In: Braunwald, E. (ed). *Heart Disease. A Textbook of Cardiovascular Medicine*, 5th edition, pp. 1105–1122. Philadelphia, USA: W.B. Saunders CO.

Saito, T., Murakami, M., Shimazaki, Y., Oobayashi, K., Matsumoto, S. & Koga, T. (2003) Association between alveolar bone loss and elevated serum C-reactive protein in Japanese men. *Journal of Periodontology* **74**, 1741–1746.

Saito, T., Shimazaki, Y., Kiyohara, Y., Kato, I., Kubo, M., Iida, M. & Yamashita, Y. (2005) Relationship between obesety, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study. *Journal of Periodontal Research* **40**, 346–353.

Salzberg, T. N., Overstreet, B. T., Rogers, J.D, Califano, J. V., Best, A.M & Schenkein, H. A. (2006) C-reactive protein levels in patients with aggressive periodontitis. *Journal of Periodontology* **77**, 933–939.

Seinost, G., Wimmer, G., Skerget, M., Thaller, E., Brodmann, M., Gasser, R., Bratschko, R. O. & Pilger, E. (2005) Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *American Heart Journal* **149**, 1050–1054.

Shakir, Y. A., Samsioe, G., Khatibi, E. A., Nyberg, P., Lidfeldt, J., Agardh, C. D. & Nerbrand, C. (2007) Health hazards in middle-aged women with cardiovascular disease: a case–control study of swedish women. The women's health in the Lund area (WHILA) study. *Journal of Womens Health* **16**, 406–414.

Shimazaki, Y., Saito, T., Kiyohara, Y., kato, I., Kubo, M., Lida, M. & Koga, T. (2004) Relationship between electrocardiographic abnormalities and periodontal disease: the Hisazama study. *Journal of Periodontology* **75**, 791–797.

Shimazaki, Y., Saito, T., Yonemoto, K., Kiyohara, Y., Iida, M. & Yamashita, Y. (2007) Relationship of metabolic syndrome to periodontal disease in Japanese women: the Hisayama Study. *Journal of Dental Research* **86**, 271–275.

Simon, A., Gariepy, J., Chironi, G., Megnien, J. L. & Levenson, J. (2002) Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *Journal of Hypertension* **20**, 159–169.

Socransky, S. S. & Haffajee, A. D. (2005) Periodontal microbial ecology. *Periodontology 2000* **38**, 135–187.

Solis, A. C., Lotufo, R. F., Pannuti, C. M., Brunheiro, E. C., Marques, A. H. & Lotufo-Neto, F. (2004) Association of periodontal disease to anxiety and depression symptoms, and psychosocial stress factors. *Journal of Clinical Periodontology* **31**, 633–638.

Spahr, A., Klein, E., Khuseyinova, N., Boeckh, C., Muche, R., Kunze, M., Rothenbacher, D., Pezeshki, G., Hoffmeister, A. & Koenig, W. (2006) 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. *Archives of Internal Medicine* **13**, 554–559.

Steptoe, A., Shamaei-Tousi, A., Gylfe, A., Henderson, B., Bergstrom, S. & Marmot, M. M. (2007) Socioeconomic status, pathogen burden, and cardiovascular disease risk. *Heart* Mai 8 **93**, 1567–1570.

Sukhija, R., Fahdi, I., Garza, L., Fink, L., Scott, M., Aude, W., Pacheco, R., Bursac, Z., Grant, A. & Mehta, J. L. (2007) Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. *American Journal of Cardiology* **99**, 879–884.

Talbert, J., Elter, J., Jared, H. L., Offenbacher, S., Southerland, J. & Wilder, R. S. (2006) The effect of periodontal therapy on TNF-alpha, IL-6 and metabolic control in type 2 diabetics. *Journal of Dental Hygieine* **80**, 7.

Taneva, E., Bogdanova, V. & Shtereva, N. (2004) Acute coronary syndrome, comorbidity, and mortality in geriatric patients. *Annals of New York Academy of Science* **1019**, 106–110.

Taylor, B. A., Tofler, G. H., Carey, H. M., Morel-Kopp, M. C., Philcox, S., Carter, T. R., Elliott, M. J., Kull, A. D., Ward, C. & Schenck, K. (2006a) Full-mouth tooth extraction lowers systemic inflammatory and thrombotic markers of cardiovascular risk. *Journal of Dental Research* **85**, 74–78.

Taylor, C. B., Conrad, A., Wilhelm, F. H., Neri, E., DeLorenzo, A., Kramer, M. A., Giese-Davis, J., Roth, W. T., Oka, R., Cooke, J. P., Kraemer, H. & Spiegel, D. (2006b) Psychophysiological and cortisol responses to psychological stress in depressed and nondepressed older men and women with elevated cardiovascular disease risk. *Psychosomatic Medicine* **68**, 538–546.

Teo, K. K., Ounpuu, S., Hawken, S., Pandey, M. R., Valentin, V., Hunt, D., Diaz, R., Rashed, W., Freeman, R., Jiang, L., Zhang, X. & Yusuf, S.INTERHEART Study Investigators (2006) Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case–control study. *Lancet* **368**, 647–658.

Terpenning, M. S., Taylor, G. W., Lopatin, D. E., Kerr, C. K., Dominguez, B. L. & Loesche, W. J. (2001) Aspiration pneumonia: dental and oral risk factors in an older veteran population. *Journal of American Geriatric Society* **49**, 557–563.

Tonetti, M. S., D'Aiuto, F., Nibali, L., Donald, A., Storry, C., Parkar, M., Suvan, J., Hingorani, A. D., Vallance, P. & Deanfield, J. (2007) Treatment of periodontitis and endothelial function. *New England Journal of Medicine* **356**, 911–920.

Tran, T., Flynn, M. J., Chen, C. & Slots, J. (1997) Absence of *Porphyromonas asaccharolytica, Bacteroides fragilis* and *Chlamydia pneumoniae* in human subgingival plaque. *Oral Microbiology and Immunolgy* **12**, 377–378.

Tsimikas, S., Willerson, J. T. & Ridker, P. M. (2006) C-reactive protein and other emerging blood biomarkers to optimize risk stratification of vulnerable patients. *Journal of American College of Cardiology* **47** (Suppl.), 19–31.

Vilkuna-Rautiainen, T., Pussinen, P. J., Roivainen, M., Petäys, T., Jousilahti, P., Hovi, T., Vartiainen, E. & Asikainen, S. (2006) Serum antibody response to periodontal pathogens and herpes simplex virus in relation to classic risk factors of cardiovascular disease. *International Journal of Epidemiology* **35**, 1486–1494.

Völzke, H., Schwahn, C., Dörr, M., Aumann, N., Felix, S. B., John, U., Rettig, R., Dören, M., Biffar, R. & Kocher, T. (2007) Inverse association between number of teeth and left ventricular mass in women. *Journal of Hypertension* **25**, 2035–2043.

Völzke, H., Wolff, B., Lüdemann, J., Guertler, L., Kramer, A., John, U. & Felix, S. B. (2006) Seropositivity for anti-Borrelia IgG antibody is independently associated with carotid atherosclerosis. *Atherosclerosis* **184**, 108–112.

Wimmer, G., Janda, M., Wieselmann-Penkner, K., Jakse, N., Polansky, R. & Pertl, C. (2002) Coping with stress: its influence on periodontal disease. *Journal of Periodontology* **73**, 1343–1351.

Woodward, M., Rumley, A., Welsh, P., MacMahon, S. & Lowe, G. (2007) A comparison of the associations between seven hemostatic or inflammatory variables and coronary heart disease. *Journal of Thrombosis and Haemostasis* **5**, 1795–1800.

Yamazaki, K., Honda, T., Domon, H., Okui, T., Kajita, K., Amanuma, R., Kudoh, C., Takashiba, S., Kokeguchi, S., Nishimura, F., Kodama, M., Aizawa, Y. & Oda, H. (2007) Relationship of periodontal infection to serum antibody levels to periodontopathic bacteria and inflammatory markers in periodontitis patients with coronary heart disease. *Clinical Experimental Immunology* **149**, 445–452.

Yamazaki, K., Honda, T., Oda, T., Ueki-Maruyama, K., Nakajima, T., Yoshie, H. & Seymour, G. J. (2005) Effect of periodontal treatment on the C-reactive protein and proinflammatory cytokine levels in Japanese periodontitis patients. *Journal of Periodontal Research* **40**, 53–58.

Yavuz, M. T., Yavuz, O., Yazici, M., Guler, S., Ozhan, H., Albayrak, S. & Coskun, A. (2006) Interaction between Chlamydia pneumoniae seropositivity, inflammation and risk factors for atherosclerosis in patients with severe coronary stenosis. *Scandinavian Journal of Clinical Laboratory Investigation* **66**, 523–534.

Yoshie, H., Kobayashi, T., Tai, H. & Galicia, J. C. (2007) The role of genetic polymorphisms in periodontitis. *Periodontology 2000* **43**, 102–132.

Yoshikawa, H., Aida, K., Mori, A., Muto, S. & Fukuda, T. (2007) Involvement of *Helicobacter pylori* infection and impaired glucose metabolism in the increase of brachial-ankle pulse wave velocity. *Helicobacter* **12**, 559–566.

Zaremba, M., Gorska, R., Suwalski, P. & Kowalski, J. (2007) Evaluation of the incidence of periodontitis associated bacteria in the atherosclerotic plaque of coronary blood vessels. *Journal of Periodontology* **78**, 322–327.

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**Clinical Relevance**

*Scientific rationale for the study:* Many studies have suggested an association between cardiovascular disease and periodontitis. The scientific rationale for the present review was to identify factors that during the last three years have been identified as possible explanations to such an association.

*Principal findings:* The review revealed that a large number of biological, social and risk behavioral factors are shared in periodontitis and cardiovascular diseases. Specifically, inflammatory markers have been studied.

*Practical implications:* Practical implications remain difficult to present due to the fact that intervention studies are not conclusive. It appears that patients with severe periodontitis are at risk of developing cardiovascular disease and dental clinician should consult cardiovascular expertise in the management of such patients.