

Increasing Evidence for an Association Between Periodontitis and Cardiovascular Disease

Ralph Stewart, MD; Malcolm West, MD

Periodontitis is a chronic inflammatory disease caused by bacterial colonization, which results in destruction of the tissues between the tooth surface and gingiva, loss of connective tissue attachment, erosion of alveolar bone, and tooth loss.¹ Periodontitis is common and increases with age. In a US survey, about half of adults aged >30 years have some periodontitis and almost 10% have severe disease.² Evidence for an association between periodontitis and atherosclerotic vascular disease, including stroke, myocardial infarction, peripheral vascular disease, abdominal aortic aneurysm, coronary heart disease, and cardiovascular death, comes from >50 prospective cohort and case control studies undertaken during the past 25 years.³⁻⁶ More recent analyses from large-cohort studies suggest new onset, and prevalent periodontitis, as well, is associated with increased coronary heart disease risk,⁷ and there is a graded association between tooth loss and stroke, cardiovascular death, and all-cause mortality in patients with stable coronary artery disease.⁸ If causal, these associations would be of great importance because of the potential that preventing or treating periodontal disease could reduce the risk of major adverse cardiovascular events.

Article see p 576

Individual studies have limitations, which include the use of imprecise measures of periodontal disease, inadequate accounting for potential confounders, and low statistical power for clinically important events. The Periodontal Disease and the Relation to Myocardial Infarction (PAROKRANK) study,⁹ published in this issue of *Circulation*, strengthens the evidence for a link between periodontal disease and first myocardial infarction. This Swedish study compared periodontal disease in 805 patients who had presented with a first myocardial infarction with 805 controls. Panoramic x-ray films were used to measure resorption of alveolar bone adjacent to the tooth root and apex. This objective measure of periodontal disease was evaluated blind to clinical information and study group in a core laboratory. At least mild periodontitis was observed in about one-third of subjects. The odds ratio for first myocardial infarction for

persons with any periodontitis in comparison with no periodontitis was 1.49 (95% confidence interval, 1.21–1.83), and, after multivariable adjustment, it was 1.28 (1.03–1.60).

Several mechanisms have been proposed to explain the association between periodontal and cardiovascular disease. Periodontitis causes both a local and systemic inflammatory and immune response, with increases in white blood cell count, C-reactive protein, fibrinogen, cell adhesion molecules, and proinflammatory cytokines.¹⁰ Treatment of periodontal disease temporarily increases the blood levels of inflammatory markers, and worsens endothelial function, probably from the release of bacteria or inflammatory cytokines into the blood stream.¹¹ However, after several weeks, inflammatory markers are lower^{11,12} and endothelial dysfunction is better than before treatment.¹¹ In the Oral Infections and Vascular Disease Epidemiology Study (INVEST) study, carotid intimal-medial thickness was associated with the volume of pathogenic bacteria on periodontal examination.¹³ Small studies have reported reduction in carotid intimal-medial thickness 6 months after treatment of severe periodontal disease.¹⁴

The systemic inflammatory or immune response to periodontal infection may increase cardiovascular risk. Also, pathogens from the mouth can enter atherosclerotic plaques via the blood stream, and this could promote an inflammatory or immune response within the atherosclerotic plaque. A diverse range of oral bacterial pathogens and bacterial DNA have been detected in atherosclerotic plaque.^{15,16} In animal models, infection with *Porphyromonas gingivalis* increases atherosclerotic plaque volume with the accumulation of cholesterol esters and inflammatory mediators.¹⁷ In humans, serum IgA antibodies to *P. gingivalis* are higher in patients with myocardial infarction than in controls.¹⁸

Although there is a strong pathophysiological rationale to support the importance of these mechanisms, it is possible the association between periodontitis and atherosclerotic vascular disease is not causal. In almost all observational studies, at least part of the association is explained by adjustment for cardiovascular risk factors. Smoking, diabetes mellitus, increasing age, and poor socioeconomic conditions are risk factors for periodontitis, and for cardiovascular disease, as well.¹ In the PAROKRANK study⁹ controls were matched to cases for age, sex, and area of residence, a surrogate indicator of socioeconomic status. However, there were modest differences in smoking, diabetes mellitus, hemoglobin A1c, and divorce or living alone between cases and controls. Adjustment for these variables about halved the strength of the association. In most previous cohort and case control studies, adjustment for known cardiovascular risk factors also only partly explained associations between periodontal disease and cardiovascular disease.^{3,5} This has been interpreted as evidence that the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand (R.S.); The University of Queensland, Brisbane, Australia (M.W.); and The Prince Charles Hospital, Brisbane, Australia (M.W.).

Correspondence to Ralph Stewart, MD, Green Lane Cardiovascular Service, Auckland City Hospital, Private Bag 92024, Victoria St West, Auckland 1142, New Zealand. E-mail rstewart@adhb.govt.nz

(*Circulation*. 2016;133:549-551.

DOI: 10.1161/CIRCULATIONAHA.115.020869.)

© 2016 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.115.020869

periodontitis accounts for the residual excess cardiovascular risk. However, the measurement of confounders is often imprecise, and some confounders may not be recognized. For example, an unhealthy dietary pattern, premature birth, adverse life stresses, and genetic predisposition could each increase the risk of both conditions, but are not measured in most studies.

Evidence of multiple common risk factors is relevant to understanding the possible common pathophysiology of atherosclerosis and periodontal disease. It also suggests that not smoking, reducing obesity, improving glucose tolerance, and addressing other common risk factors could benefit both conditions. Limited evidence suggests that statins may decrease periodontal inflammation, possibly by decreasing cholesterol deposits adjacent to periosteal bone which may enhance the inflammatory response.^{19,20} Recognition that genes linked to chromosome 9p21, and related to transforming growth factor beta regulation, predispose to periodontitis, and to coronary artery disease, as well, provides further evidence that common pathophysiological pathways are important for the 2 diseases.²¹

Should treatment of periodontal disease be recommended to reduce the risk of cardiovascular disease? No, or only with reservations; because the key evidence needed, that treatment of periodontal disease lowers the risk of major adverse cardiovascular events, is missing. For this a large randomized clinical trial is needed. To date, only a pilot study, the Periodontitis and Vascular Events (PAVE) investigation, has reported.²² This randomized trial compared the effects of a single full-mouth scaling and root planing with community care in 301 patients with stable coronary artery disease. Major cardiovascular events were assessed over 6 to 25 months. The study had low statistical power and, as expected, the impact of the intervention on clinical outcomes was inconclusive. The strength of associations between periodontitis and cardiovascular events is modest, with hazard ratios of ≈ 1.20 in adjusted models from meta-analyses of prospective cohort studies.^{3,5} A clinical trial would need to be very large to detect the plausible effects of treatment to reduce periodontal disease on major cardiovascular events. Periodontitis is a chronic condition, so a long-term approach, rather than a single treatment, would be needed to achieve sustained improvement in periodontal health. Periodontal disease is reduced by daily tooth brushing and flossing, and by scaling and planing by a dentist or dental hygienist. These are currently recommended as part of good oral health, independent of the possible benefits for cardiovascular disease. Evaluating the effectiveness of interventions for periodontal disease to reduce major cardiovascular events in a large randomized clinical trial will therefore be challenging.

In 2012, an American Heart Association scientific statement⁴ concluded that there is no class A or B evidence that periodontal disease causes atherosclerotic vascular disease, and cautioned that statements that imply a causative association, or that specific therapeutic interventions may be useful, are unwarranted.⁴ This caution remains appropriate. The PAROKRANK study⁹ adds to the strong evidence for an association between periodontitis and myocardial infarction, but does not prove causation. However, knowledge that the

association is at least partly explained by common risk factors is important, because it provides further evidence that strategies to reduce cardiovascular risk, such as the American Heart Association's Life's Simple 7, are also likely to benefit other determinants of good health.

Disclosures

None.

References

- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. *Lancet*. 2005;366:1809–1820. doi: 10.1016/S0140-6736(05)67728-8.
- Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ; CDC Periodontal Disease Surveillance workgroup: James Beck (University of North Carolina, Chapel Hill, USA), Gordon Douglass (Past President, American Academy of Periodontology), Roy Page (University of Washin. Prevalence of periodontitis in adults in the United States: 2009 and 2010. *J Dent Res*. 2012;91:914–920. doi: 10.1177/0022034512457373.
- Leng WD, Zeng XT, Kwong JS, Hua XP. Periodontal disease and risk of coronary heart disease: an updated meta-analysis of prospective cohort studies. *Int J Cardiol*. 2015;201:469–472. doi: 10.1016/j.ijcard.2015.07.087.
- Lockhart PB, Bolger AF, Papapanou PN, Osinbowale O, Trevisan M, Levison ME, Taubert KA, Newburger JW, Gornik HL, Gewitz MH, Wilson WR, Smith SC Jr, Baddour LM; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association?: a scientific statement from the American Heart Association. *Circulation*. 2012;125:2520–2544. doi: 10.1161/CIR.0b013e31825719f3.
- Humphrey LL, Fu R, Buckley DI, Freeman M, Helfand M. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. *J Gen Intern Med*. 2008;23:2079–2086. doi: 10.1007/s11606-008-0787-6.
- Lafon A, Pereira B, Dufour T, Rigouby V, Giroud M, Béjot Y, Tubert-Jeannin S. Periodontal disease and stroke: a meta-analysis of cohort studies. *Eur J Neurol*. 2014;21:1155–61, e66. doi: 10.1111/ene.12415.
- Yu YH, Chasman DI, Buring JE, Rose L, Ridker PM. Cardiovascular risks associated with incident and prevalent periodontal disease. *J Clin Periodontol*. 2015;42:21–28. doi: 10.1111/jcpe.12335.
- Vedin O, Hagstrom E, Budaj A, Denchev S, Harrington RA, Koenig W, Soffer J, Sritara P, Stebbins A, Stewart RH, Swart HP, Viigimaa M, Vinereanu D, Wallentin L, White HD, Held C. Tooth loss is independently associated with poor outcomes in stable coronary heart disease (published online ahead of print December 16, 2015). *Eur J Prev Cardiol*. doi: 10.1177/2047487315621978. <http://cpr.sagepub.com/content/early/2015/12/14/2047487315621978>.long. Accessed December 24, 2015.
- Rydén L, Buhlin K, Ekstrand E, de Faire U, Gustafsson A, Holmer J, Kjellström B, Lindahl B, Norhammar A, Nygren A, Näsmän P, Rathnayake N, Svenungsson E, Klinge B. Periodontitis increases the risk of a first myocardial infarction. a report from the PAROKRANK Study. *Circulation*. 2016;133:576–583. doi: 10.1161/CIRCULATIONAHA.115.020324.
- Mustapha IZ, Debrey S, Oladubu M, Ugarte R. Markers of systemic bacterial exposure in periodontal disease and cardiovascular disease risk: a systematic review and meta-analysis. *J Periodontol*. 2007;78:2289–2302. doi: 10.1902/jop.2007.070140.
- Tonetti MS, D' Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med*. 2007;356:911–920. doi: 10.1056/NEJMoa063186.
- Teeuw WJ, Slot DE, Susanto H, Gerdes VE, Abbas F, D' Aiuto F, Kastelein JJ, Loos BG. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. *J Clin Periodontol*. 2014;41:70–79. doi: 10.1111/jcpe.12171.
- Desvarieux M, Demmer RT, Rundek T, Boden-Albala B, Jacobs DR Jr, Papapanou PN, Sacco RL; Oral Infections and Vascular Disease Epidemiology Study (INVEST). Relationship between periodontal disease, tooth loss, and carotid artery plaque: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Stroke*. 2003;34:2120–2125. doi: 10.1161/01.STR.0000085086.50957.22.

14. Piconi S, Trabattoni D, Luraghi C, Perilli E, Borelli M, Pacei M, Rizzardini G, Lattuada A, Bray DH, Catalano M, Sparaco A, Clerici M. Treatment of periodontal disease results in improvements in endothelial dysfunction and reduction of the carotid intima-media thickness. *FASEB J*. 2009;23:1196–1204. doi: 10.1096/fj.08-119578.
15. Ott SJ, El Mokhtari NE, Musfeldt M, Hellmig S, Freitag S, Rehman A, Kühbacher T, Nikolaus S, Namsolleck P, Blaut M, Hampe J, Sahly H, Reinecke A, Haake N, Günther R, Krüger D, Lins M, Herrmann G, Fölsch UR, Simon R, Schreiber S. Detection of diverse bacterial signatures in atherosclerotic lesions of patients with coronary heart disease. *Circulation*. 2006;113:929–937. doi: 10.1161/CIRCULATIONAHA.105.579979.
16. Fernandes CP, Oliveira FA, Silva PG, Alves AP, Mota MR, Montenegro RC, Burbano RM, Seabra AD, Lobo Filho JG, Lima DL, Soares Filho AW, Sousa FB. Molecular analysis of oral bacteria in dental biofilm and atherosclerotic plaques of patients with vascular disease. *Int J Cardiol*. 2014;174:710–712. doi: 10.1016/j.ijcard.2014.04.201.
17. Hayashi C, Viereck J, Hua N, Phinikaridou A, Madrigal AG, Gibson FC 3rd, Hamilton JA, Genco CA. Porphyromonas gingivalis accelerates inflammatory atherosclerosis in the innominate artery of ApoE deficient mice. *Atherosclerosis*. 2011;215:52–59. doi: 10.1016/j.atherosclerosis.2010.12.009.
18. Pussinen PJ, Alfthan G, Tuomilehto J, Asikainen S, Jousilahti P. High serum antibody levels to Porphyromonas gingivalis predict myocardial infarction. *Eur J Cardiovasc Prev Rehabil*. 2004;11:408–411.
19. Subramanian S, Emami H, Vucic E, Singh P, Vijayakumar J, Fifer KM, Alon A, Shankar SS, Farkouh M, Rudd JH, Fayad ZA, Van Dyke TE, Tawakol A. High-dose atorvastatin reduces periodontal inflammation: a novel pleiotropic effect of statins. *J Am Coll Cardiol*. 2013;62:2382–2391. doi: 10.1016/j.jacc.2013.08.1627.
20. Rosenberg DR, Andrade CX, Chaparro AP, Inostroza CM, Ramirez V, Violant D, Nart J. Short-term effects of 2% atorvastatin dentifrice as an adjunct to periodontal therapy: a randomized double-masked clinical trial. *J Periodontol*. 2015;86:623–630. doi: 10.1902/jop.2015.140503.
21. Schaefer AS, Richter GM, Groessner-Schreiber B, Noack B, Nothnagel M, El Mokhtari NE, Loos BG, Jepsen S, Schreiber S. Identification of a shared genetic susceptibility locus for coronary heart disease and periodontitis. *PLoS Genet*. 2009;5:e1000378. doi: 10.1371/journal.pgen.1000378.
22. Offenbacher S, Beck JD, Moss K, Mendoza L, Paquette DW, Barrow DA, Couper DJ, Stewart DD, Falkner KL, Graham SP, Grossi S, Gunsolley JC, Madden T, Maupome G, Trevisan M, Van Dyke TE, Genco RJ. Results from the Periodontitis and Vascular Events (PAVE) Study: a pilot multicentered, randomized, controlled trial to study effects of periodontal therapy in a secondary prevention model of cardiovascular disease. *J Periodontol*. 2009;80:190–201. doi: 10.1902/jop.2009.080007.

KEY WORDS: Editorials ■ cardiovascular diseases ■ periodontitis ■ risk factors ■ tooth