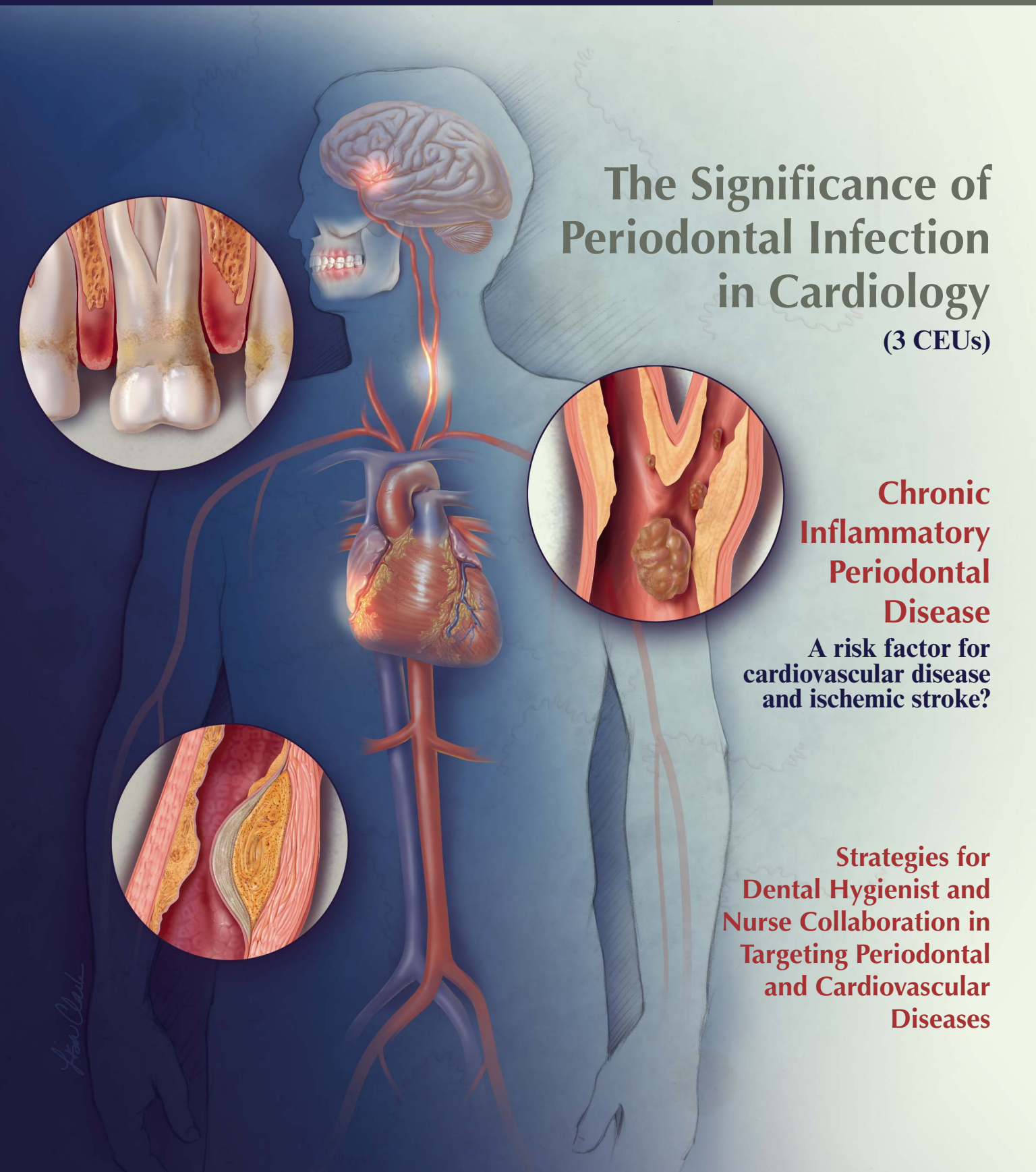
GRAND ROUNDS
in Oral-Systemic Medicine™

PennWell

February 2006, Vol. 1, No. 1



The Significance of Periodontal Infection in Cardiology

(3 CEUs)

Chronic Inflammatory Periodontal Disease

A risk factor for cardiovascular disease and ischemic stroke?

Strategies for Dental Hygienist and Nurse Collaboration in Targeting Periodontal and Cardiovascular Diseases

Think all toothpastes work the same?

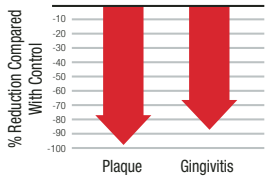
Take a deeper look.

Colgate Total® is proven to fight oral inflammation. Scientific evidence has linked oral inflammation to systemic health diseases such as cardiovascular and other diseases throughout the body[1-4]

Only Colgate Total® contains triclosan, and only triclosan fights oral inflammation in 2 important ways[1-3,5,6]

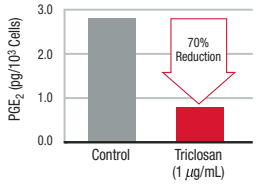
Kills plaque bacteria for a full 12 hours[5]

Up to 98% More Plaque Reduction[1,2]*; up to 88% More Gingivitis Reduction[1,2]*



Reduces the level of inflammatory mediators that may play a role in systemic health[3,4]

70% Reduction in PGE_2—a Key Mediator[6†]



"Recent evidence suggests a strong relationship between periodontal inflammatory disease and systemic diseases such as cardiovascular disease. It is now generally accepted that inflammation plays an important role…"[7]
—Sheilesh, et al. *Compendium.* 2004.

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Visit **colgateprofessional.com** for free patient samples.

Colgate Total® is the only FDA-approved toothpaste for plaque and gingivitis.

1. Volpe AR, et al. *J Clin Dent.* 1996;7(suppl):S1-S14. **2.** Davies RM, et al. *J Clin Periodontol.* 2004;31:1029-1033. **3.** Gaffar A, et al. *J Clin Periodontol.* 1995;22:480-484. **4.** Scannapieco FA. *Compendium.* 2004;7(suppl 1):16-25. **5.** Amornchat C, et al. *Mahidol Dent J.* 2004;24:103-111. **6.** Modéer T, et al. *J Clin Periodontol.* 1996;23:927-933. **7.** Sheilesh D, et al. *Compendium.* 2004;7(suppl 1):26-37.

*vs ordinary fluoride toothpaste. †in vitro.

C53248

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GRAND ROUNDS
in Oral-Systemic Medicine™

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Statement of Editorial Purpose: The editorial purpose of *Grand Rounds in Oral-Systemic Medicine*™ is to raise awareness of the importance of the relationship between oral and systemic health, and advance the understanding of oral-systemic science and its appropriate integration into the clinical practice of mainstream dentistry and medicine by providing editorial that:

- Compels members of the dental and medical communities to embrace the growing body of science called oral-systemic medicine and accept the uncertainty of its ongoing evolution.
- Translates/transfers credible and relevant scientific findings and scholarly thought related to oral-systemic medicine into authoritative editorial that is educational and engages all sectors of the health-care professions (i.e., physicians and nurses, dentists and hygienists and allied health-care providers).
- Stimulates collaboration and innovative thinking on how to transcend professional boundaries to integrate clinical protocols that include application of oral-systemic medicine in everyday patient care.

Policy on Submission of Manuscripts: The opportunity to contribute to the editorial mission of *Grand Rounds in Oral-Systemic Medicine*™ is offered to author candidates by honorary invitation. As such, unsolicited manuscripts are generally not accepted. Manuscripts published in *Grand Rounds in Oral-Systemic Medicine*™ are written by authors who are invited to contribute to this body of knowledge based upon their academic, research or clinical expertise, from both dentistry and medicine, in specific subject matters that pertain to oral-systemic medicine.

ARESTIN® is indicated as an adjunct to scaling and root planing (SRP) procedures for reduction of pocket depth in patients with adult periodontitis. ARESTIN® may be used as part of a periodontal program which includes good oral hygiene, and scaling and root planing.

ARESTIN® contains minocycline, a tetracycline derivative, and therefore should not be used in children and in pregnant or nursing women. The use of drugs of the tetracycline class during tooth development may cause permanent discoloration of the teeth.

The most common treatment-emergent adverse events were headache (9.0%), infection (7.6%), flu syndrome (5.0%), and pain (4.3%). These occurred at a similar rate to SRP and SRP + placebo.

ORAPHARMA, INC.

References: 1. Williams RC. Periodontal disease. *N Engl J Med* 1990;322:373-382. **2.** Williams RC, Paquette DW, Offenbacher S, et al. Treatment of periodontitis by local administration of minocycline microspheres: a controlled trial. *J Periodontol* 2001;72:1535-1544. **3.** ARESTIN® (minocycline HCl) 1 mg Microspheres [Prescribing Information]. Warminster, PA: OraPharma, Inc; 2004. **4.** Data on file. OraPharma, Inc, Warminster, PA, 2002.

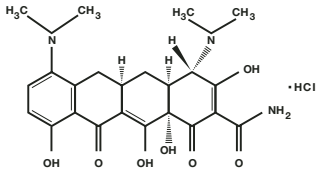
Please see full Prescribing Information on last page.


All beautiful work deserves a solid foundation.
Insist on a healthy foundation for your dental work. Treat infected gums with ARESTIN® + SRP.
Certain harmful bacteria can infect the periodontium—the foundation of your patients' oral health. Periodontal disease is the #1 cause of adult tooth loss in the United States.[1]
Regardless of the type of procedure—cosmetic, restorative, or hygiene—it is important to check for periodontal disease first to make sure your dental work never rests on an infected foundation. ARESTIN® (minocycline HCl) 1 mg Microspheres is an effective locally administered antibiotic that fights periodontal infection right where it starts—inside the infected pockets.
When used with scaling and root planing (SRP), ARESTIN®:
• Significantly reduces pocket depth versus SRP alone[2,3]
• Maintains therapeutic drug levels for up to 21 days[4]
• Can be used during your subgingival scaling procedures[3]
Before you build your next beautiful smile, consider the foundation that supports your dental work.
FOR MORE INFORMATION ABOUT ARESTIN®, PLEASE VISIT WWW.ARESTIN.COM/GR
Arestin®
minocycline HCl 1mg
Microspheres
Fight infection right where it starts.

ARESTIN®
(minocycline hydrochloride) Microspheres, 1 mg

DESCRIPTION

ARESTIN® (minocycline hydrochloride) Microspheres is a subgingival sustained-release product containing the antibiotic minocycline hydrochloride incorporated into a bioresorbable polymer, Poly (glycolide-co-dl-lactide) or PGLA, for professional subgingival administration into periodontal pockets. Each unit-dose cartridge delivers minocycline hydrochloride equivalent to 1 mg of minocycline free base. The molecular formula of minocycline hydrochloride is $C_{23}H_{27}N_3O_7$. HCl, and the molecular weight is 493.94. The structural formula of minocycline hydrochloride is:



CLINICAL PHARMACOLOGY

Microbiology

Minocycline, a member of the tetracycline class of antibiotics, has a broad spectrum of activity.[1] It is bacteriostatic and exerts its antimicrobial activity by inhibiting protein synthesis.[1] In vitro susceptibility testing has shown that the organisms *Porphyromonas gingivalis, Prevotella intermedia, Fusobacterium nucleatum, Eikenella corrodens,* and *Actinobacillus actinomycetemcomitans,* which are associated with periodontal disease, are susceptible to minocycline at concentrations of ≤8 µg/mL[2]; qualitative and quantitative changes in plaque microorganisms have not been demonstrated in patients with periodontitis, using this product.

The emergence of minocycline-resistant bacteria in single-site plaque samples was studied in subjects before and after treatment with ARESTIN at 2 centers. There was a slight increase in the numbers of minocycline-resistant bacteria at the end of the 9-month study period, however, the number of subjects studied was small and the clinical significance of these findings is unknown.

The emergence of minocycline-resistant bacteria and changes in the presence of *Candida albicans* and *Staphylococcus aureus* in the gastrointestinal tract were studied in subjects treated with ARESTIN in one phase 3 study. No changes in the presence of minocycline-resistant bacteria or *C albicans* or *S aureus* were seen at the end of the 56-day study period.

Pharmacokinetics

In a pharmacokinetic study, 18 patients (10 men and 8 women) with moderate to advanced chronic periodontitis were treated with a mean dose of 46.2 mg (25 to 112 unit doses) of ARESTIN. After fasting for at least 10 hours, patients received subgingival application of ARESTIN (1 mg per treatment site) following scaling and root planing at a minimum of 30 sites on at least 8 teeth. Investigational drug was administered to all eligible sites ≥5 mm in probing depth. Mean dose normalized saliva AUC and C_{max} were found to be approximately 125 and 1000 times higher than those of serum parameters, respectively.

Clinical Studies

In 2 well-controlled, multicenter, investigator-blind, vehicle-controlled, parallel-design studies (3 arms), 748 patients (study OPI-103A = 368, study OPI-103B = 380) with generalized moderate to advanced adult periodontitis characterized by a mean probing depth of 5.90 and 5.81 mm, respectively, were enrolled. Subjects received 1 of 3 treatments: (1) scaling and root planing, (2) scaling and root planing + vehicle (bioresorbable polymer, PGLA), and (3) scaling and root planing + ARESTIN. To qualify for the study, patients were required to have 4 teeth with periodontal pockets of 6 to 9 mm that bled on probing. However, treatment was administered to all sites with mean probing depths of 5 mm or greater. Patients studied were in good general health. Patients with poor glycemic control or active infectious diseases were excluded from the studies. Retreatment occurred at 3 and 6 months after initial treatment, and any new site with pocket depth ≥5 mm also received treatment. Patients treated with ARESTIN were found to have statistically significantly reduced probing pocket depth compared with those treated with SRP alone or SRP + vehicle at 9 months after initial treatment, as shown in Table 1.

Table 1: Probing Pocket Depth at Baseline and Change in Pocket Depth at 9 Months From 2 Multicenter US Clinical Trials

Time	Study OPI-103A N=368			Study OPI-103B N=380		
	SRP Alone n=124	SRP + Vehicle n=123	SRP + ARESTIN n=121	SRP Alone n=126	SRP + Vehicle n=126	SRP + ARESTIN n=128
PD (mm) at Baseline, Mean ± SE	5.88± 0.04	5.91± 0.04	5.88± 0.04	5.79± 0.03	5.82± 0.04	5.81± 0.04
PD (mm) Change From Baseline at 9 Months, Mean ± SE	-1.04 ±0.07	-0.90 ±0.54	-1.20*†† ±0.07	-1.32 ±0.07	-1.30 ±0.07	-1.63**†† ±0.07

SE = standard error; SRP = scaling and root planing; PD = pocket depth.
Significantly different from SRP *($P \leq 0.05$); **($P \leq 0.001$).
Significantly different from SRP + vehicle †($P \leq 0.05$); ††($P \leq 0.001$).

In these 2 studies, an average of 29.5 (5-114), 31.7 (4-137), and 31 (5-108) sites were treated at baseline in the SRP alone, SRP + vehicle, and SRP + ARESTIN groups, respectively. When these studies are combined, the mean pocket depth change at 9 months was -1.18 mm, -1.10 mm, and -1.42 mm for SRP alone, SRP + vehicle, and SRP+ ARESTIN, respectively.

Table 2: Numbers (percentage) of Pockets Showing a Change of Pocket Depth ≥2 mm at 9 Months From 2 Multicenter US Clinical Trials

	Study OPI-103A			Study OPI-103B		
	SRP Alone	SRP + Vehicle	SRP + ARESTIN	SRP Alone	SRP + Vehicle	SRP + ARESTIN
Pockets ≥2 mm (% of total)	1046 (31.1%)	927 (25.7%)	1326 (36.5%)	1692 (42.2%)	1710 (40.0%)	2082 (51.0%)
Pockets ≥3 mm (% of total)	417 (12.4%)	315 (8.7%)	548 (15.1%)	553 (13.8%)	524 (12.3%)	704 (17.3%)

SRP + ARESTIN resulted in a greater percentage of pockets showing a change of PD ≥2 mm and ≥3 mm compared to SRP alone at 9 months, as shown in Table 2.

Table 3: Mean Pocket Depth Changes (SE) in Subpopulations, Studies 103A and 103B Combined

	SRP Alone	SRP + Vehicle	SRP + ARESTIN
Smokers	n = 91 -0.96± 0.09 mm	n = 90 -0.98± 0.07 mm	n = 90 -1.24± 0.09 mm**
Nonsmokers	n = 159 -1.31± 0.06 mm	n = 159 -1.17± 0.07 mm	n = 159 -1.53± 0.06 mm**
Patients >50 YOA	n = 21 -1.07± 0.09 mm	n = 81 -0.92± 0.08 mm	n = 107 -1.42± 0.08 mm**
Patients ≤50 YOA	n = 167 -1.24± 0.06 mm	n = 168 -1.19± 0.06 mm	n = 142 -1.43± 0.07 mm*
Patients With CV Disease	n = 36 -0.99± 0.13 mm	n = 29 -1.06± 0.14 mm	n = 36 -1.56± 0.14 mm**
Patients W/O CV Disease	n = 214 -1.22± 0.06 mm	n = 220 -1.11± 0.05 mm	n = 213 -1.40± 0.06 mm**

SRP = scaling and root planing; YOA = years of age; CV = cardiovascular.
*SRP vs SRP + ARESTIN $P \leq 0.05$; **SRP vs SRP + ARESTIN $P \leq 0.001$.

In both studies, the following patient subgroups were prospectively analyzed: smokers, patients over and under 50 years of age, and patients with a previous history of cardiovascular disease. The results of the combined studies are presented in Table 3. In smokers, the mean reduction in pocket depth at 9 months was less in all treatment groups than in nonsmokers, but the reduction in mean pocket depth at 9 months with SRP + ARESTIN® was significantly greater than with SRP + vehicle or SRP alone.

Table 4: Mean Pocket Depth Change in Patients With Mean Baseline PD ≥5 mm, ≥6 mm, and ≥7 mm at 9 Months From 2 Multicenter US Clinical Trials

	Study OPI-103A			Study OPI-103B		
Mean Baseline Pocket Depth	SRP Alone	SRP + Vehicle	SRP + ARESTIN	SRP Alone	SRP + Vehicle	SRP + ARESTIN
≥5 mm (n)	-1.04 mm (124)	-0.90 mm (123)	-1.20 mm* (121)	-1.32 mm (126)	-1.30 mm (126)	-1.63 mm* (128)
≥6 mm (n)	-0.91 mm (34)	-0.77 mm (46)	-1.40 mm* (45)	-1.33 mm (37)	-1.46 mm (40)	-1.69 mm* (25)
≥7 mm (n)	-1.10 mm (4)	-0.46 mm (5)	-1.91 mm (3)	-1.72 mm (3)	-1.11 mm (3)	-2.84 mm (2)

*Statistically significant comparison between SRP + ARESTIN and SRP alone.

The combined data from these 2 studies also show that for pockets 5 mm to 7 mm at baseline, greater reductions in pocket depth occurred in pockets that were deeper at baseline.

INDICATIONS AND USE

ARESTIN is indicated as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis. ARESTIN may be used as part of a periodontal maintenance program which includes good oral hygiene, and scaling and root planing.

CONTRAINDICATIONS

ARESTIN should not be used in any patient who has a known sensitivity to minocycline or tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY BROWN). This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, OR IN PREGNANT OR NURSING WOMEN, UNLESS THE POTENTIAL BENEFITS ARE CONSIDERED TO OUTWEIGH THE POTENTIAL RISKS. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracyclines are used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

The use of ARESTIN in an acutely abscessed periodontal pocket has not been studied and is not recommended.

While no overgrowth by opportunistic microorganisms, such as yeast, were noted during clinical studies, as with other antimicrobials, the use of ARESTIN may result in overgrowth of nonsusceptible microorganisms including fungi. The effects of treatment for greater than 6 months has not been studied.

ARESTIN should be used with caution in patients having a history of predisposition to oral candidiasis. The safety and effectiveness of ARESTIN has not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

ARESTIN has not been clinically tested in immunocompromised patients (such as those immunocompromised by diabetes, chemotherapy, radiation therapy, or infection with HIV).

If superinfection is suspected, appropriate measures should be taken.

ARESTIN has not been clinically tested in pregnant women.

ARESTIN has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

Information for Patients

After treatment, patients should avoid eating hard, crunchy, or sticky foods for 1 week and postpone brushing for a 12-hour period, as well as avoid touching treated areas. Patients should also postpone the use of interproximal cleaning devices for 10 days after administration of ARESTIN. Patients should be advised that although some mild to moderate sensitivity is expected during the first week after SRP and administration of ARESTIN, they should notify the dentist promptly if pain, swelling, or other problems occur.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Dietary administration of minocycline in long-term tumorigenicity studies in rats resulted in evidence of thyroid tumor production. Minocycline has also been found to produce thyroid hyperplasia in rats and dogs. In addition, there has been evidence of oncogenic activity in rats in studies with a related antibiotic, oxytetracycline (ie, adrenal and pituitary tumors). Minocycline demonstrated no potential to cause genetic toxicity in a battery of assays which included a bacterial reverse mutation assay (Ames test), an in vitro mammalian cell gene mutation test ($L5178Y/TK^{+/-}$ mouse lymphoma assay), an in vitro mammalian chromosome aberration test, and an in vivo micronucleus assay conducted in ICR mice.

Fertility and general reproduction studies have provided evidence that minocycline impairs fertility in male rats.

Teratogenic Effects: Pregnancy Category D. (See **WARNINGS**.)

Labor and Delivery

The effects of tetracyclines on labor and delivery are unknown.

Nursing Mothers

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS**.)

Pediatric Use

Since adult periodontitis does not affect children, the safety and effectiveness of ARESTIN® in pediatric patients cannot be established.

ADVERSE REACTIONS

The most frequently reported nondental treatment-emergent adverse events in the 3 multicenter US trials were headache, infection, flu syndrome, and pain.

Table 5: Adverse Events (AEs) Reported in ≥3% of the Combined Clinical Trial Population of 3 Multicenter US Trials by Treatment Group

	SRP Alone N=250	SRP + Vehicle N=249	SRP + ARESTIN N=423
Number (%) of Patients Treatment-emergent AEs	62.4%	71.9%	68.1%
Total Number of AEs	543	589	987
Periodontitis	25.6%	28.1%	16.3%
Tooth Disorder	12.0%	13.7%	12.3%
Tooth Caries	9.2%	11.2%	9.9%
Dental Pain	8.8%	8.8%	9.9%
Gingivitis	7.2%	8.8%	9.2%
Headache	7.2%	11.6%	9.0%
Infection	8.0%	9.6%	7.6%
Stomatitis	8.4%	6.8%	6.4%
Mouth Ulceration	1.6%	3.2%	5.0%
Flu Syndrome	3.2%	6.4%	5.0%
Pharyngitis	3.2%	1.6%	4.3%
Pain	4.0%	1.2%	4.3%
Dyspepsia	2.0%	0	4.0%
Infection Dental	4.0%	3.6%	3.8%
Mucous Membrane Disorder	2.4%	0.8%	3.3%

The change in clinical attachment levels was similar across all study arms, suggesting that neither the vehicle nor ARESTIN compromise clinical attachment.

DOSAGE AND ADMINISTRATION

ARESTIN is provided as a dry powder, packaged in a unit-dose cartridge, which is inserted into a cartridge handle to administer the product. The oral health care professional removes the disposable cartridge from its pouch and connects the cartridge to the handle mechanism (see Figures 1-3). ARESTIN is a variable dose product, dependent on the size, shape, and number of pockets being treated. In US clinical trials, up to 121 unit-dose cartridges were used in a single visit and up to 3 treatments, at 3-month intervals, were administered in pockets with pocket depth of 5 mm or greater.

Figure 1

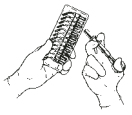


Figure 2

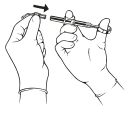


Figure 3

The administration of ARESTIN does not require local anesthesia. Professional subgingival administration is accomplished by inserting the unit-dose cartridge to the base of the periodontal pocket and then pressing the thumb ring in the handle mechanism to expel the powder while gradually withdrawing the tip from the base of the pocket. The handle mechanism should be sterilized between patients. ARESTIN does not have to be removed, as it is bioresorbable, nor is an adhesive or dressing required.

HOW SUPPLIED

ARESTIN® (minocycline hydrochloride) Microspheres, 1 mg is supplied in unit doses of 12 cartridges in one tray (NDC 65976-100-24) packaged with desiccant in a heat-sealed foil-laminated resealable pouch. There are 2 pouches in each box. Each unit-dose cartridge contains the product identifier "OP-1."

Storage Conditions

Store at 20° to 25°C (68° to 77°F)/60% RH: excursions permitted to 15° to 30°C (59° to 86°F). Avoid exposure to excessive heat.

Rx only

Manufactured for OraPharma, Inc.

Distributed by: Cord Logistics, Inc.
15 Ingram Boulevard
La Vergne, TN 37086

REFERENCES: 1. Stratton CW, Lorian V. Mechanisms of action of antimicrobial agents: general principles and mechanisms for selected classes of antibiotics. In: *Antibiotics in Laboratory Medicine.* 4th ed. Baltimore, Md: Williams and Wilkins; 1996. **2.** Slots J, Rams TE. Antibiotics in periodontal therapy: advantages and disadvantages. *J Clin Periodontol.* 1990;17:479-493.

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GRAND ROUNDS in Oral-Systemic Medicine™

OPPORTUNITIES MAXIMIZED OR MISSED?


Casey Hein


Charley Cobb

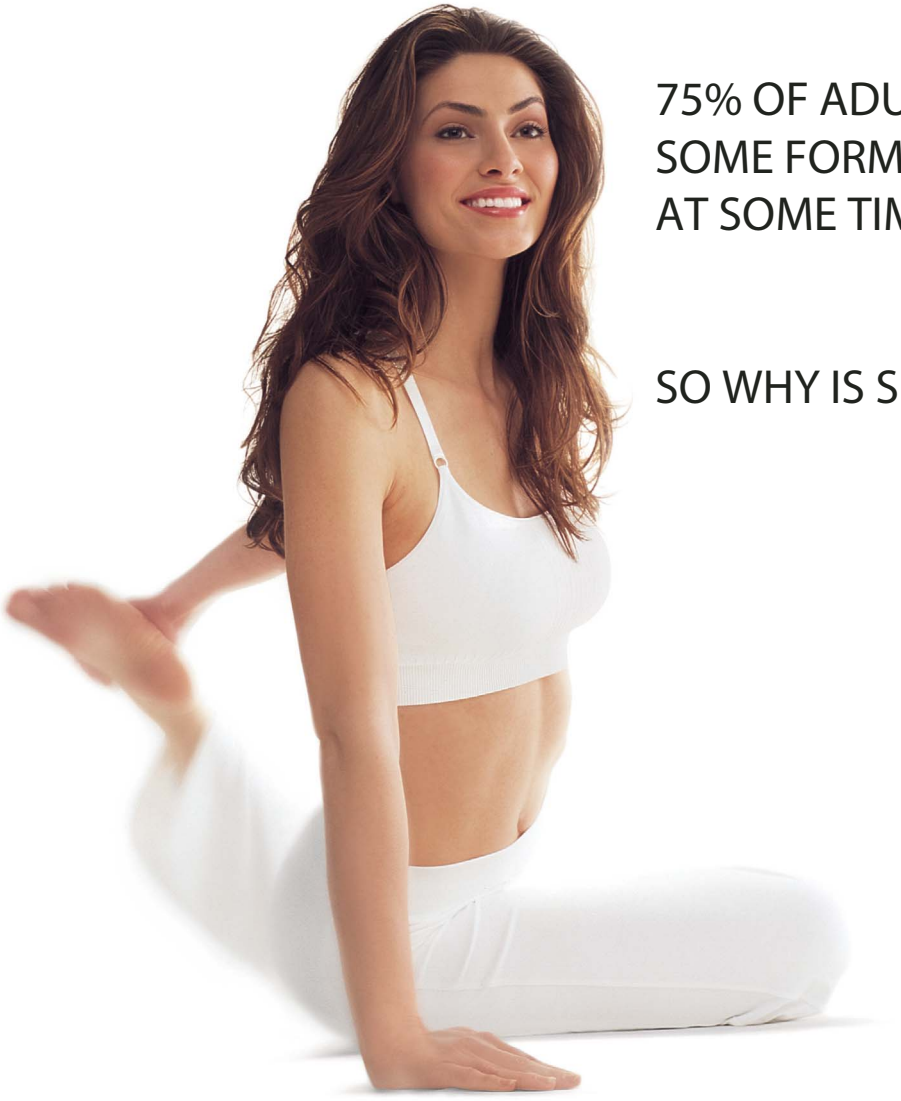
Without question, the last decade of research in oral-systemic medicine has provided us with extraordinary scientific findings. Yet, as once stated, "Scientific study that is not translated and used in daily practice ultimately is wasted."[1] To that end, ensuring that important scientific study such as oral-systemic medicine is translated for adoption into daily practice is no small challenge. In fact, it has been estimated that it takes about 20 years for findings of new research or novel technologies to be fully adopted and implemented into the health-care system. Our experiences mirror the reality of that statement. In discussions with practitioners from around the country, the area of education which is most consistently cited as being inadequate is oral-systemic medicine and its implementation. "Just tell us what to do with this information..." characterizes the feedback from readers and those who attend continuing-education courses. And this is where we started. The impetus behind this new editorial concept called *Grand Rounds in Oral-Systemic Medicine*™ was our mutual pursuit of a reliable mechanism to transfer the findings of credible research of oral-systemic medicine into mainstream dentistry. We thank PennWell for supporting our vision.

One of the many compelling statements made in the Surgeon General's Report on *Oral Health in America* was the following, "...the concept of oral health as secondary and separate from general health is deeply engrained in American consciousness, and hence may be the pivotal and most difficult barrier to overcome."[2] Overcoming this hurdle requires refocusing the public's attention on the importance of oral health, but first providers of dental and medical care must believe this message themselves. Our hope is that *Grand Rounds* will be a catalyst to move mainstream dentistry and medicine towards greater awareness and appreciation of the importance of oral health in maintaining systemic health. Dental practitioners have an unprecedented opportunity to join our medical colleagues to advance novel health promotion, disease prevention, and disease management strategies, all of which have the potential to significantly alter the disease trajectory of many serious chronic diseases and conditions. The truth is providers of medical and dental care are both entrusted with the systemic health of their patients. Those health-care professionals who do not recognize this body of emerging science called oral-systemic medicine will miss a valuable window of opportunity for therapeutic intervention.

The need to change nondental health-care providers' perception of the importance of oral health was also discussed in *Oral Health in America*.[3] The Surgeon General challenged medical and dental health-care providers that they "should be ready, willing, and able to work in collaboration to provide optimal health care for their patients," and employ more targeted intervention strategies for those at high risk.[3] *Grand Rounds* proposes to meet this challenge by circulating the journal not only to dentists and dental hygienists but to a group of 10,000 physicians and nurses (2006) and delivering innovative editorial dedicated to:

- Compelling members of the dental and medical communities to embrace the growing body of science called oral-systemic medicine and accept the uncertainty of its ongoing evolution.
- Translating/transferring credible and relevant scientific findings and scholarly thought related to oral-systemic medicine into authoritative editorial that is educational and engages all sectors of the health-care professions.
- Stimulating collaboration and innovative thinking on how to transcend professional boundaries to integrate clinical protocols that include application of oral-systemic medicine in everyday patient care.

To help build collaborative models of care with the medical community, a number of highly respected medical specialists have joined what some have called a "world class advisory board" for *Grand Rounds in Oral-Systemic Medicine*™. It goes



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1. ADA News Release, American Dental Association, September, 2001

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without saying that we are very honored that so many of the icons in research, education, and private practice could see the same vision, and were willing to offer their expertise in advancing this important editorial mission. It is important to note that the most serious responsibility members of the advisory board have is to ensure the scientific integrity of the publication by preventing incorrect or over-reaching statements on research findings.

Grand Rounds has been created as a peer-reviewed, quarterly publication with each issue dedicated to an area of oral-systemic medicine which has relevance to specific disease relationships. In this inaugural issue, the relationship of periodontal disease and cardiovascular disease is discussed. Dr. Maria Ryan's guest editorial is a wonderful way to jump-start this new publication. A synoptic review of the literature, co-authored by Gapski and Cobb, provide readers with the "bottom line" regarding the state of the research related to the relationship between periodontal disease and cardiovascular disease. Shanies and Hein provide a cardiologist's and dental hygienist's perspective on the importance of ensuring periodontal wellness in cardiology, offering reassurance to readers that cardiologists may indeed be starting to look at the threat of periodontal disease a little differently.

The article that proposes strategies for dental hygienist and nurse collaboration in targeting periodontal and cardiovascular diseases will challenge the paradigms of those within both dentistry and medicine — and that is precisely what is meant to happen in *Grand Rounds*. In an editorial about inflammation, arthrosclerosis, and ischemic events published in 1997 in the *New England Journal of Medicine*, Maseri wrote: "... it is easier to study the details of accepted paradigms than it is to develop new hypotheses, just as it was easier to map the visible face of the moon than it was to explore its hidden side." Likewise, we gain nothing by denying the exploration of a new paradigm and refusing to consider its potential in health promotion and disease prevention.

The implementation tools we have included in this inaugural issue are helpful in the application of this body of knowledge. In this issue and future issues, readers will be provided material for patient education and highly relevant information to establish dentists' communication wtih physicians regarding at-risk patients.

Given the input of a multitude of individuals within dentistry and medicine — from education, clinical research, and private practice — there seems to be no end to the subjects we have been asked to address in future issues of *Grand Rounds*. A complimentary, fully digitized edition of this journal is available at www.thesystemiclink.com, which extends the access of *Grand Rounds* to clinicians and educators around the world. The second issue is devoted to the discussion of the bi-directional relationship between periodontal disease and diabetes.

Each encounter we have with a patient is an important window of opportunity. This includes an opportunity to promote a healthy lifestyle, an opportunity to educate a patient about risk factors for oral and systemic diseases, or an opportunity to get a whole family in treatment. This window also includes an opportunity to refer a patient to a risk-reduction program or to triage a patient to a specialist for treatment of a chronic condition that may increase risk for other diseases or amplify existing conditions. Some practitioners won't see this as a window of opportunity. As a result, an opportunity to deliver high-quality care will be missed. At the point of care, the choice is ours. Our hope is that *Grand Rounds* will help dental and medical professionals maximize the opportunity to integrate important oral-systemic medicine into everday patient care — an opportunity that none of us should miss.

Sincerely,

Casey Hein, BSDH, MBA
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caseyh@pennwell.com

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References

1. Vinicor, F. Is diabetes a public health disorder? *Diabetes Care* 17(S1):22-27, 1994
2. National Institute of Dental and Craniofacial Research. Facing the Challenge NIDCR Strategic Plan. Available at: http://www.nidcr.nih.gov/AboutNIDCR/StrategicPlan/FacingTheChallenge.htm. Accessed Dec 20, 2005.
3. U.S. Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General*. Rockville, Md: U.S. Department of Health and Human Services, National Institute of Dental and Cranial Research, National Institutes of Health; 2000.
4. Maseri I. Inflammation, atherosclerosis, and ischemic events — exploring the hidden side of the moon. *N Engl J Med* 1997 Apr 3;336(14):1014-6.

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GRAND ROUNDS WITH DR. MARIA RYAN

Maria E. Ryan, DDS, PhD, Professor and Director of Clinical Research, State University of New York at Stony Brook School of Dental Medicine

It is with great excitement and enthusiasm for this new publication, *Grand Rounds in Oral-Systemic Medicine*™, that I am writing about my experience with hospital grand rounds. During the past decade, data has been mounting in support of the connections between oral and systemic health: certain systemic conditions increase a person's risk for developing a variety of oral diseases and, conversely, poor oral health — particularly periodontal disease characterized by infection and associated inflammation — increases the risk for developing many systemic disorders.[1,2] Recent reports regarding the ill effects of chronic long-term oral inflammation have supported the importance of achieving and maintaining healthy oral tissues.[3]

The main issue regarding the existing and emerging information is the paucity of knowledge transfer. In a world of information overload, the message often is lost or the receiver of the information does not know how to process and use it. I believe this publication will provide a missing link that will enable health-care providers to incorporate the latest epidemiological findings, along with results of preclinical and clinical research studies for disease management and intervention, into their clinical practices.

Many years ago, I was confronted by a new patient who had a variety of oral and general health problems. She came to my office with an article that had appeared in *USA Today*.[4] The patient was astonished by the findings presented in the article that linked oral health to systemic diseases such as diabetes, cardiovascular disease, stroke, and adverse pregnancy outcomes. She expressed dismay over the fact that multiple specialists in the medical and dental professions never had shared this information with her. As health-care providers, we recognize that patients are more informed today than ever. But, through this patient encounter, I came to realize that many practitioners either are not aware or unable to use this emerging new information in a way that would be useful to both practitioners and their patients.

Shortly after this revelation, I was asked to participate in a symposium entitled "Diabetes: Meeting the Challenge," held in Galveston, Texas.[5] I was honored to be invited to speak on "The Impact of Periodontal Diseases on the Diabetic Patient" with a diverse group of health-care providers.[5] I listened intently as slides of flow charts listing all of the providers necessary for the adequate care and management of patients with diabetes were projected. Unfortunately, there was not any mention of an oral health-care provider on these slides. I was impressed by the presentations given by the physicians who represented multiple disciplines such as internal medicine, endocrinology, ophthalmology, psychiatry, gastroenterology, nephrology, cardiology, neurology, and dermatology. Diabetology even had emerged as a subspecialty of endocrinology. The nurses, nurse practitioners, physician assistants, nutritionists, psychologists, and podiatrists all spoke eloquently about their roles in managing this complex disease.

I anxiously awaited my turn, which was to come on the last day at the last hour of the two-day conference. At this point, I was thrilled to get to the podium to share information that was unknown to the majority of the audience. Most were surprised by the fact that patients with uncontrolled diabetes are at greater risk for developing periodontitis. They also were surprised to learn that untreated periodontitis can have a significant impact on the ability of health-care providers to gain metabolic control of patients with diabetes ... and may even impede their ability to manage or even prevent certain complications.[6] Data also was emerging that connected an oral long-term complication of

diabetes — periodontitis — with an increased risk for the development of additional long-term complications, such as nephropathy and angiopathy.[7] These have most recently have been linked to mortality in Type 2 diabetic individuals.[8]

As I left this meeting, I recognized the need to disseminate the emerging oral health message to as many health-care providers and patients as possible. Many of my colleagues in academia already had embarked on this journey, and I had decided to join them. Patients are extremely interested in understanding the connections between their oral and systemic health. Initially, I presented data to support oral-systemic links to very receptive groups of dentists and dental hygienists in a lecture titled, "To Head Off Disease, Start at the Top."[9]

Once the Surgeon General's report on *Oral Health in America* was released, it was time to approach the physicians.[10] Through the years, I have been invited to present at hospital grand rounds for endocrinology, obstetrics and gynecology, pediatrics, cardiology, and general clinical research. My experiences in response to these grand round presentations have been enlightening. My impression is that the oral-systemic health message is well received by all of these groups, but it may be the first time that some in the audience are receiving the information. This is surprising to me because many of the findings presented regarding oral-systemic connections have been published in medical as well as dental journals. A second area of feedback from the medical providers has been that when referring patients to dental providers for the diagnosis and treatment of oral disorders, some dental providers have proceeded with hesitation because of the complexity of the patient's medical needs. Some dental providers have expressed uncertainty as to the risk for systemic disease that the dental condition may present.

Clearly, the message that oral infection and inflammation can present a significant challenge to the patient must be reinforced and presented to a wide array of practitioners in a straight-forward manner that translates into actions which can be taken in their clinical practices. There is still much work to be done in this area to establish treatment protocols for high-risk patients. As emerging information is shared with practitioners in publications such as this one, both medical and dental professionals will be empowered to make treatment decision based on the latest findings. It is my hope that this journal will serve as a source of important new information and data regarding oral-systemic connections, and that it also will provide clinicians with a forum to discuss the steps necessary to incorporate this knowledge into clinical practice for the benefit of all patients.

References

1. Genco RJ, Stamm JW. 1997 Sunstar-Chapel Hill Symposium on Periodontal Diseases and Human Health: New Directions in Periodontal Medicine. *J Periodontol*. 1998;3(1):1-387.
2. Rose LF, Genco RJ, Cohen DW, et al. *Periodontal Medicine*. Hamilton, Ontario, Canada: BC Decker, Inc; 2000:1-294.
3. Genco RJ, Armitage GC. 2003 Workshop on Contemporary Science in Clinical Periodontics. *J Periodontol*. 2005;8(1):1-78.
4. Sternberg S. Chronic tooth infections can kill more than smile. *USA Today*. 1998;Apr 14 (Life):1D.
5. Ryan M. The Impact of Periodontal Diseases in the Diabetic Patient. Diabetes: Meeting the Challenge symposium. Galveston, Tex: October 21 and 22, 1999. Sponsored by Medivision Media Group.
6. Diabetes and oral health: treating the patient with diabetes mellitus. *J Am Dent Assoc*. 2003;134:1S-64S.
7. Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J Clin Periodontol*. 1996;23(3 Pt 1):194-202.
8. Saremi A, Nelson RG, Tulloch-Reid M, et al. Periodontal disease and mortality in type 2 diabetes. *Diabetes Care*. 2005;28(1):27-32.
9. Ryan M. To Head Off Disease, Start at the Top. Lecture 2000.
10. Satcher D. US Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General*. May 2000. Available at: http://www.surgeongeneral.gov/library/oralhealth/. Accessed Nov 18, 2005.

Literature Review

CHRONIC INFLAMMATORY PERIODONTAL DISEASE

A RISK FACTOR FOR CARDIOVASCULAR DISEASE AND ISCHEMIC STROKE?

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GRAND ROUNDS
in Oral-Systemic Medicine™

Ricardo Gapski, DDS, MS,† and
Charles M. Cobb, DDS, PhD‡

Abstract
This literature review discusses the findings of more recent studies investigating the relationship between chronic inflammatory periodontal disease and risk for cardiovascular disease and stroke. The intensity of inflammation in moderate and severe chronic periodontitis is clearly sufficient to induce a systemic response. The systemic response is commonly expressed by elevated serum levels of inflammatory mediators and acute-phase reactants like C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), serum amyloid A, fibrinogen, and haptoglobin. The presence of chronic oral inflammation may enhance atherosclerotic pathogenesis through one or more mechanisms, such as stimulation of humoral and cell-mediated inflammatory pathways, bacteremia leading to direct interaction of periodontal pathogenic microbes with the arterial wall, and increases in circulating mediators of inflammation.

There are many clinical studies and investigations using animal models that, when collectively considered, indicate a significant association of periodontitis with cardiovascular and cerebrovascular diseases. Although a direct causal relationship remains to be demonstrated, it appears that at the very least, periodontitis represents a systemic inflammatory burden that facilitates atheroma formation, which may lead to a cardiovascular or cerebrovascular event.

Citation: Gapski R, Cobb CM. Chronic inflammatory periodontal disease: A risk factor for cardiovascular disease and ischemic stroke? *Grand Rounds in Oral-Sys Med*. 2006;1:14-22.

(A complimentary copy of this article may be downloaded at www.thesystemiclink.com.)

Key words: Periodontitis, inflammation, inflammatory mediators, bacteria, cardiovascular disease, ischemic stroke

Hujoel and colleagues[1] have calculated that among individuals with chronic periodontitis, the surface area of the dentogingival epithelium exposed to potential bacterial invasion and/or infiltration of antigenic microbial components ranges between 8 cm^2 and 20 cm^2. Thus, it is not surprising that a breach of this epithelial barrier is a common occurrence in chronic and aggressive periodontitis, and is likely to result in systemic dissemination of microbes, antigens, and mediators of inflammation.

Locally, bacteria and their byproducts of metabolism stimulate a cellular immune response represented by a dense infiltration of neutrophils, macrophages, and various lymphoid cells. These cells and the host connective tissue cells associated with the inflammatory lesion are stimulated to synthesize and release proinflammatory cytokines and prostanoids — interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), prostaglandin E_2 (PGE_2), and various matrix metalloproteinases (MMPs) — which play a role in the destruction of alveolar bone and connective tissues that furnish support to the teeth.[2] In addition to being a major cause of adult tooth loss, recent studies suggest that chronic and aggressive periodontitis may constitute an independent risk factor for

† Department of Periodontics, University of Missouri - Kansas City, School of Dentistry
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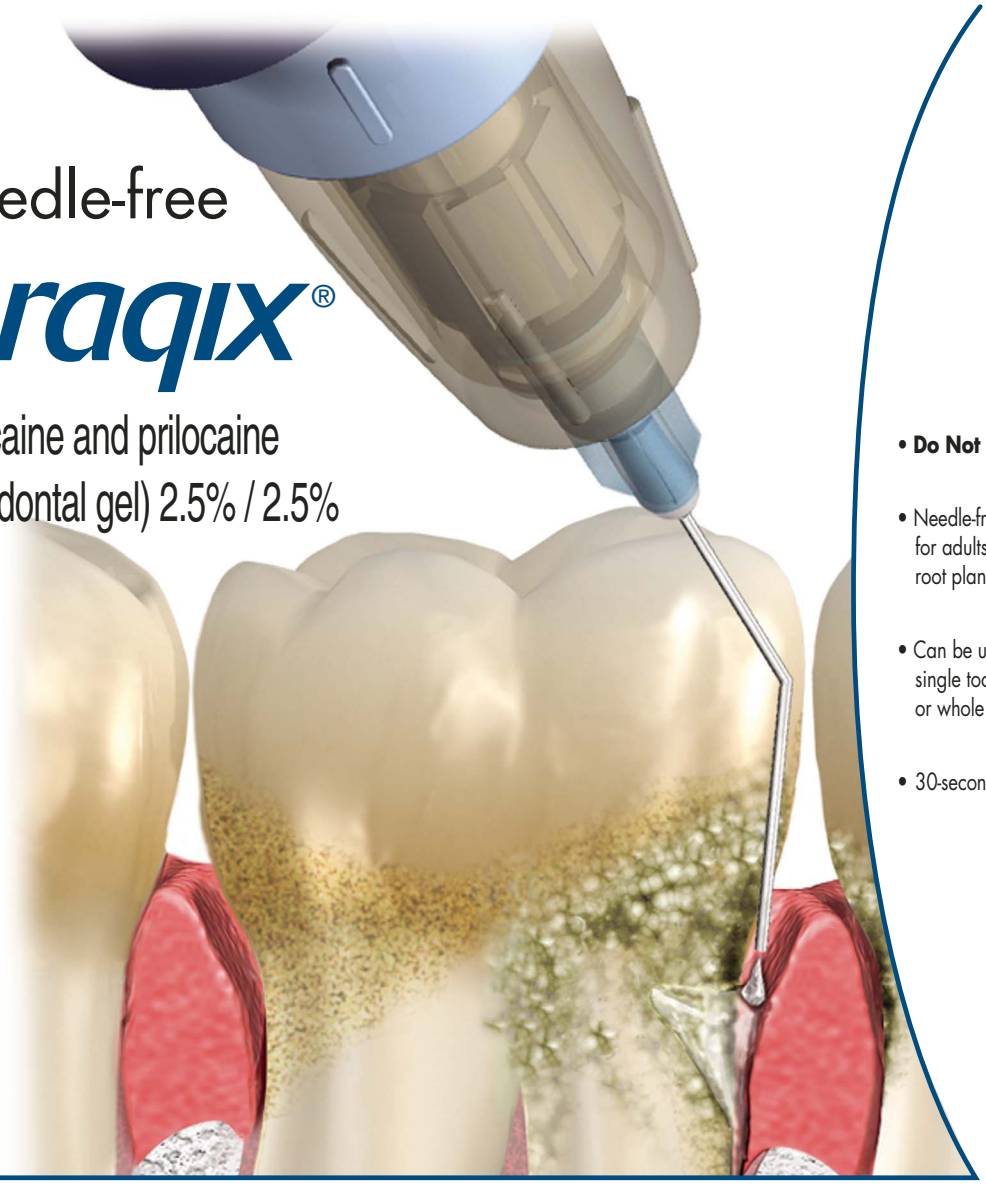

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Oraqix® is contraindicated in patients with hypersensitivity to amide type local anesthetics or to any other product component.

WARNINGS
Prilocaine can cause elevated methemoglobin levels particularly in conjunction with methemoglobin-inducing agents. Methemoglobinemia has been reported in a few cases in association with lidocaine treatment. Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methemoglobinemia are more susceptible to drug-induced methemoglobinemia. Oraqix® should not be used in those patients with congenital or idiopathic methemoglobinemia and in infants under the age of twelve months who are receiving treatment with methemoglobin-inducing agents. Signs and symptoms of methemoglobinemia may be delayed some hours after exposure. Initial signs and symptoms of methemoglobinemia are characterized by a slate grey cyanosis seen in, e.g., buccal mucous membranes, lips and nail beds. In severe cases symptoms may include central cyanosis, headache, lethargy, dizziness, fatigue, syncope, dyspnea, CNS depression, seizures, dysrhythmia and shock. Methemoglobinemia should be considered if central cyanosis unresponsive to oxygen therapy occurs, especially if metHb-inducing agents have been used. Calculated oxygen saturation and pulse oximetry are inaccurate in the setting of methemoglobinemia. The diagnosis can be confirmed by an elevated methemoglobin level measured with co-oximetry. Normally, metHb levels are <1%, and cyanosis may not be evident until a level of at least 10% is present. The development of methemoglobinemia is generally dose related. The individual maximum level of metHb in blood ranged from 0.8% to 1.7% following administration of the maximum dose of 8.5 g Oraqix®.

Management of Methemoglobinemia: Clinically significant symptoms of methemoglobinemia should be treated with a standard clinical regimen such as a slow intravenous injection of methylene blue at a dosage of 1-2 mg/kg given over a five minute period.

Patients taking drugs associated with drug-induced methemoglobinemia such as sulfonamides, acetaminophen, acetanilide, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, and quinine are also at greater risk for developing methemoglobinemia.

Treatment with Oraqix® should be avoided in patients with any of the above conditions or with a previous history of problems in connection with prilocaine treatment.

PRECAUTIONS
General:
DO NOT INJECT
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Allergic and anaphylactic reactions associated with lidocaine or prilocaine can occur. These reactions may be characterized by urticaria, angioedema, bronchospasm, and shock.

Eye contact with Oraqix® should be avoided. Animal studies have demonstrated severe eye irritation. Corneal irritation and potential abrasion may occur. If eye contact occurs, immediately rinse the eye with water or saline and protect it until normal sensation returns. In addition, the patient should be evaluated by an ophthalmologist.

Oraqix® should be used with caution in patients with a history of drug sensitivities, especially if the etiologic agent is uncertain.

Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations of lidocaine and prilocaine.

Information for Patients: Patients are cautioned to avoid injury to the treated area, or exposure to extreme hot or cold temperatures, until complete sensation has returned.

Drug Interactions: Oraqix® should be used with caution in combination with dental injection anesthesia, other local anesthetics, or agents structurally related to local anesthetics, e.g., Class 1 antiarrhythmics such as tocainide and mexiletine, as the toxic effects of these drugs are likely to be additive and potentially synergistic.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:
Carcinogenesis - Chronic oral toxicity studies of o-toluidine, a metabolite of prilocaine, have shown that this compound is a carcinogen in both mice and rats. The tumors associated with o-toluidine included hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional-cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/ adenomas in female rats. These findings were observed at the lowest tested dose of 150 mg/kg/day or greater over two years (estimated daily exposures in mice and rats were approximately 6 and 12 times, respectively, the estimated exposure to o-toluidine at the maximum recommended human dose of 8.5g of Oraqix® gel on a mg/m2 basis).

o-Toluidine, a metabolite of prilocaine, was positive in Escherichia coli DNA repair and phage-induction assays. Urine concentrates from rats treated orally with 300 mg/kg o-toluidine were mutagenic to Salmonella typhimurium in the presence of metabolic activation.

USE IN PREGNANCY:
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Treatment of rabbits with 15 mg/kg (180 mg/m2) produced evidence of maternal toxicity and evidence of delayed fetal development, including a non-significant decrease in fetal weight (7%) and an increase in minor skeletal anomalies (skull and sternebral defects, reduced ossification of the phalanges). The effects of lidocaine and prilocaine on post-natal development was examined in rats treated for 8 months with 10 or 30 mg/kg, s.c. lidocaine or prilocaine (60 mg/m2 and 180 mg/m2 on a body surface area basis, respectively up to 1.4-fold the maximum recommended exposure for a single procedure). This time period encompassed 3 mating periods. Both doses of either drug significantly reduced the average number of pups per litter surviving until weaning of offspring from the first 2 mating periods. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Oraqix® should be used during pregnancy only if the benefits outweigh the risks.

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Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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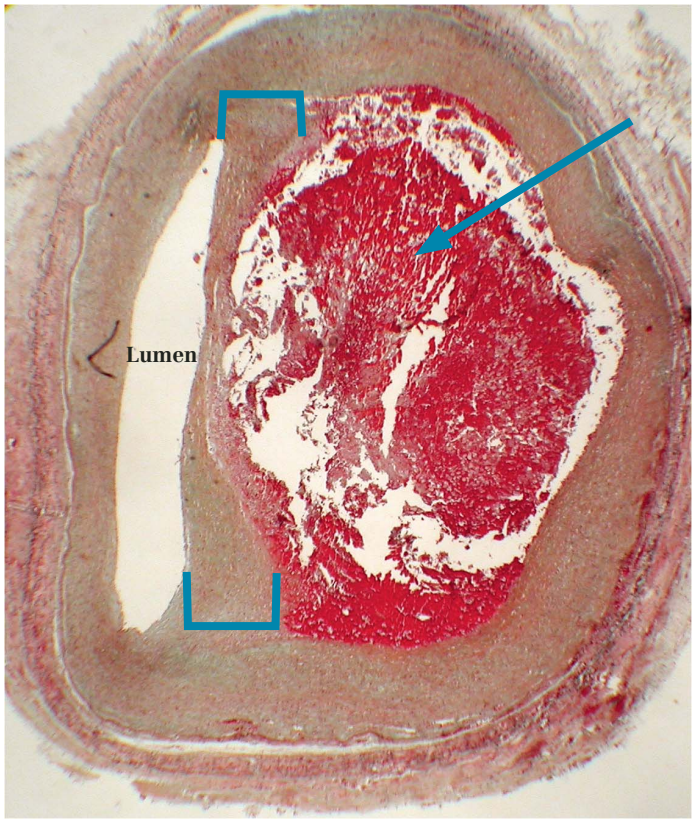

Figure 1

Histologic cross-section of a coronary artery exhibiting extensive atheroma formation consisting of fibrous cap (bracket) and infiltration of cholesterol (arrows).

Specimen provided by Dr. Joseph C. Whitt, Department of Oral and Maxillofacial Pathology, University of Missouri-Kansas City School of Dentistry, Kansas City, Mo. Movat's stain; original magnification x25.

cardiovascular disease and ischemic stroke.[3-14] However, other investigators have suggested that periodontitis may not be an independent risk factor but does represent a comorbid condition (i.e., a disease that coexists with other diseases because of a common causal factor). In some studies, smoking is shown as the common causal factor in periodontitis, cardiovascular disease, and ischemic stroke[15,16] In spite of the apparent differences in theory, periodontitis may add to the cumulative systemic insult derived from repeated exposures to other chronic inflammatory diseases during an individual's lifetime.[17-22]

Inflammatory markers

A variety of inflammation markers have been correlated to increasing severity of periodontitis, atherosclerosis, and ischemic stroke. For example, inflammation is characterized by the production of cell-derived mediators of inflammation, such as IL-6, TNF-α, and PGE_2. In turn, their systemic distribution via the vascular circulatory system induces the production of liver-derived markers of a systemic inflammatory reaction, such as c-reactive protein (CRP), serum amyloid A, fibrinogen, and haptoglobin. CRP is a particularly sensitive systemic marker of systemic inflammation. A serum CRP concentration of >10 mg/L is generally indicative of significant inflammatory disease. Compared with healthy controls, individuals with severe periodontitis are consistent in their expression of elevated serum CRP levels.[23-27] Other markers of inflammation elevated in cases of periodontitis, either in serum or gingival crevicular fluid, include haptoglobin,[23] fibrinogen,[27] serum amyloid A, IL-1, IL-6, IL-8, PGE_2, TNF-α, and various MMPs.[2]

Noack and colleagues[24] reported that the degree of increases in CRP levels in patients with periodontitis, when adjusted for confounding modifying factors, is dependent on the severity of the disease. The authors also demonstrated a strong relationship between elevated CRP levels and the presence of several periodontal pathogenic microbes, i.e., *Porphyromonas gingivalis (P. gingivalis), Prevotella intermedia (P. intermedia), Campylobacter rectus (C. rectus),* and *Tannerella forsythia (T. forsythia)*, thereby establishing an association between periodontal infections and elevated CRP levels. Serum levels of CRP, IL-6, fibrinogen, and IL-8 are also elevated in patients with unstable angina, myocardial infarction,[22] and ischemic stroke,[28] with higher levels being correlated to increasingly poor prognoses.[22]

Periodontal pathogenic microbes and vascular disease

Animal studies —

Following reports in medical literature that relate *Chlamydia pneumoniae* and cytomegalovirus infections to the etiology of atherosclerosis, Hzaraszthy and colleagues[29] reported that 40 of 50 (80 percent) endarterectomy specimens taken from patients with carotid stenosis were positive for periodontal pathogens, such as *T. forsythia, P. gingivalis, P. intermedia, or Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans)*. In addition, almost 60 percent of the specimens were positive for two or more of the target microbes. Thus, their hypothesis that oral microbes associated with severe chronic periodontitis may gain access to the systemic circulatory system and, thereby, play a role in development of atherosclerosis was supported.

Additional support for this hypothesis soon followed in a series of animal studies. Using a mouse experimental model, Kesavalu and colleagues[30] were able to induce pro-inflammatory cytokine expression (IL-1β, IL-6, and TNF-α) following subcutaneous injection of *P. gingivalis* and *A. actinomycetemcomitans*. Li and colleagues[31] demonstrated that repeated systemic inoculation of *P. gingivalis* resulted in significant macrophage-rich atherosclerotic plaque formation in the proximal aorta and aortic-tree vessels in a mouse model. Jain and colleagues[32] induced aortic lipid deposition in rabbits through a high fat-content diet while simultaneously inducing periodontitis in the mandibular molars in one experimental group. When compared with control animals in the second group without periodontitis, those animals with periodontal disease exhibited significantly greater accumulations of lipid (atheroma formation) in the aorta. Indeed, there was a positive correlation between the severity of periodontal disease and the extent of aortic lipid deposition.

Additionally, it has been demonstrated that whole cells of *P. gingivalis* and endotoxin derived from *P. gingivalis* are both capable of inducing, in vitro, foam-cell formation of mouse-derived macrophages when cultured in the presence of human low-density lipoprotein (LDL).[33] In another study, *P. gingivalis* and its endotoxin-laden vesicles promoted LDL binding to macrophages and promoted macrophage modification of native LDL, which plays an important role in foam-cell formation and the pathogenesis of atherosclerosis.[34] Further, Lalla and colleagues[35] demonstrated that mice, when infected with *P. gingivalis*, exhibited severe periodontitis, presence of *P. gingivalis* DNA in 22 percent of aortic biopsy specimens, and elevated serum IL-6 levels. Lastly, Gibson and colleagues[36] have shown that mice, when challenged with *P. gingivalis*, exhibited increased atherosclerotic plaque formation, which could be prevented by immunization against *P. gingivalis*.

Human studies —

Because of the purported roles of *P. gingivalis* and *A. actinomycetemcomitans* in severe chronic periodontitis, Pussinen and colleagues[37, 38] chose to analyze the association of coronary heart disease and ischemic stroke to antibody levels specific for these two microbes. They found that coronary disease was more prevalent among edentulous than dentate subjects (19.8 percent vs. 12.1 percent, respectively). Further, coronary disease was more common among patients with positive antibody levels (seropositive) for *P. gingivalis* as compared with those who were antibody-negative (seronegative) — 14 percent vs. 9.7 percent, respectively. Seropositive individuals had a risk ratio of 1.6 for an ischemic stroke event. In addition, subjects with a history of stroke or coronary heart disease were more often seropositive for *P. gingivalis* and had an risk ratio of 2.6 for a secondary stroke event. These results suggest that periodontal infections, or response of the host against such infections, may play a role in the pathogenesis of coronary heart disease and ischemic stroke.

Kuramitsu and colleagues[39, 40] studied the interaction of *P. gingivalis* with human umbilical vein endothelial cells and were able to show that *P. gingivalis* was capable of inducing increased expression of a cytokine — monocyte chemoattractant protein-1 — that recruits monocytes. In addition, *P. gingivalis* increases the expression of a protein that facilitates attachment of monocytes to endothelial cells, called intercellular adhesion molecule-1 (ICAM-1). Lastly, *P. gingivalis* increases the cellular production of elastase/gelatinase (MMP-9), which has been implicated in atheroma plaque rupture.[40] The authors hypothesize that *P. gingivalis*-endothelial cell interactions may lead to recruitment and attachment of monocytes to the endothelial lining of blood vessels, thereby initiating vascular atheroma formation.

Research on the relationship of inflammation to cardiovascular disease has begun to focus on heat shock protein 60 (HSP60), which is strongly immunogenic. Further, HSP60 appears to be a signaling molecule that can mediate and influence a range of inflammatory responses. For example, both bacterial and host HSP60 activate human vascular endothelial cell expression of intercellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1). In addition, both types of HSP60 activate monocytes and/or macrophages to secrete IL-6 and TNF-α. Because of a high degree of sequence homology (molecular similarity) between bacterial and human HSP60, it has been suggested that HSP60 may be involved in human autoimmune disease mechanisms (i.e., the host immune system primed by HSP60 of bacterial origin can interact with its human host counterpart in gingival connective tissue or arterial walls).[41]

Yamazaki and colleagues[42] have examined the link between chronic periodontitis, atherosclerosis, and HSP60. Using both human and *P. gingivalis* HSP60 as the antigen, they compared humoral immune responses in atherosclerotic patients with responses in patients with

chronic periodontitis and in healthy patients. Results showed antibody levels to both human and *P. gingivalis* HSP60 were highest in atherosclerosis patients, followed by periodontitis patients, and lowest in healthy patients. Similar results have also been reported by Chung and colleagues.[43]

Desvarieux and colleagues[44] reported a direct relationship, independent of CRP levels, between thickness of the tunica intima and tunica media of the carotid artery (indicating atherosclerotic plaque formation) and the presence of five periodontal microbial pathogens, *P. gingivalis, A. actinomycetemcomitans, T. forsythia, Treponema denticola (T. denticola)*, and *Micromonas micros*. Shortly thereafter, Kozarov and colleagues[45] reported the presence of viable invasive *A. actinomycetemcomitans* and *P. gingivalis* in cells from human carotid artery atherosclerotic plaque. Marques da Silva and colleagues[46] used DNA probe techniques to examine 56 samples from aortic aneurysms taken from 51 patients for the presence of four periodontal microbial pathogens *(A. actinomycetemcomitans, P. gingivalis, T. denticola,* and *T. forsythia)*. They detected bacterial DNA in 89.2 percent of the specimens. However, *A. actinomycetemcomitans* was detected in only four specimens (7.1 percent), and all specimens were negative for the other three microbes. An explanation for this seeming paradox is found in a previous study by Marques da Silva and colleagues[47] in which anaerobic culture and electron microscopy techniques were used to demonstrate the presence of several common oral microbes, such as *Streptococcus mitis, Actinomyces naeslundii*, and *Actinomyces viscosus*.

Recently, Fiehn and colleagues[48] identified DNA from periodontal pathogenic microbes in atherosclerotic plaques that were removed from carotid and femoral arteries. DNA of *P. intermedia* was consistently detected, but *P. gingivalis* DNA was noted only sporadically. Interestingly, when cultured under anaerobic conditions, none of the tissue specimens yielded growth of oral bacteria. Additionally, Dögan and colleagues[49] compared the total bacterial number in subgingival plaque samples from periodontitis patients with and without a history of recent myocardial infarction. The authors reported that bacterial levels were elevated in only those patients with a history of myocardial infarction, leading the authors to suggest that increased loads of subgingival bacteria may present a risk for systemic health.

Current data does not indicate a direct involvement of the bacteria in development of aortic aneurysms. However, a dominant feature in the pathogenesis of aortic aneurysms is the proteolytic degradation of the aortic wall by MMPs. The expression of collagenase (MMP-1 and MMP-13) and elastase/gelatinase (MMP-2, MMP-9, and MMP-12) is increased in aortic aneurysm tissues. Theoretically, the presence of bacteria in a vascular wall lesion induces a localized inflammation with the inherent induction of various cytokines, primary mediators of inflammation that, in turn, stimulate MMP expression by host cells, eventually leading to an aortic aneurysm.

Clinical studies

Two studies in 1989 reported statistically significant relationships between oral health and myocardial and cerebral infarction.[50,51] Since that time, several studies have reported epidemiological associations between chronic periodontitis and cardiovascular and cerebrovascular disease.[4-8, 52-56] It is now obvious that periodontal disease and atherosclerotic plaque-related diseases have several risk factors in common, such as smoking, diabetes, elevated levels of serum CRP, etc. Because of overlapping risk factors, it remains difficult to demonstrate a direct causal relationship between chronic periodontitis and cardiovascular and cerebrovascular disease. However, this does not minimize the role of chronic periodontitis as an inflammatory risk factor in atherosclerosis and its sequelae.[10]

Many studies have examined the role of chronic periodontitis as an independent risk factor and an "infectious burden" in general; taken collectively, they indicate a significant association with atheroma formation (Figure 1) and ischemic stroke.[11,14,19,26,28,57-62] It has been suggested that periodontal inflammation may contribute to a prothrombotic state via recurrent bacteremias, platelet activation, and elevated clotting factors, thereby increasing the risk of embolism formation and ischemic stroke.[14]

Other studies suggest that it is highly unlikely that a single infectious agent or inflammatory disease plays a unique role in atheroma development. It is more likely that the risk of developing atherosclerosis is related to the number of inflammatory disease events to which an individual has been exposed.[61-63] One can argue that periodontitis represents a chronic inflammatory infection that may exist for years, thereby exposing the patient to a continuous microbial insult and all of the

inherent metabolic events associated with inflammation. Given such a scenario, moderate and severe chronic periodontitis represent an important risk factor for the development of atherosclerosis leading to cardiovascular and cerebrovascular disease. Thus, it is clinically relevant that three recent studies have reported that periodontal therapy consisting of scaling and root planing and subgingival delivery of antimicrobial agents is effective in reducing levels of serum inflammatory markers, specifically CRP, IL-6, and TNF-α.[64-66]

Conclusion

Inflammation in the vessel wall plays an essential role in the initiation and progression of atherosclerosis, the erosion or disruption of vascular atheromas, and eventual rupture of such plaques.[22] The collective body of literature suggests that immune activation in cases of severe chronic periodontitis results in the concomitant systemic dissemination of gram-negative microbes, antigens and endotoxins, and mediators of inflammation. The dissemination of these factors, in turn, appears to promote inflammation of the arteries involving the cardiovascular and cerebrovascular systems, leading to atherosclerosis, and ultimately initiating an acute coronary event or ischemic stroke, with circulating levels of the inflammatory markers reflecting the clinical course of the condition.

The general hypothesis that chronic infections, such as periodontitis, can contribute to the development of atherosclerosis and, thereby, cardiovascular disease and ischemic stroke, is based on the following observations:

- Infectious agents can directly interact with the cellular components of the tunica intima and tunica media of vessels.
- There is systemic dissemination of cytokines and mediators of inflammation because of chronic inflammatory disease, such as periodontitis.
- There is an increased expression of cytokines, mediators of inflammation, and cellular adhesion molecules resulting in local endothelial dysfunction.

Although the studies cited in this review point to a role for periodontal disease in the development of cardiovascular and cerebrovascular disease, it remains to be shown that treatment of periodontal disease will prevent atherosclerotic events. Currently, there is insufficient data to differentiate between the role of a direct infection of the vascular wall and stimulation of a proinflammatory state by periodontitis. In spite of these shortcomings, it is critical to test the hypothesis that intensive treatment of inflammatory periodontal disease and long-term maintenance will have a positive impact on the clinical course of atherosclerotic-related diseases.

References

1. Hujoel PP, White BA, Garcia RI, et al. The dentogingival epithelial surface area revisited. *J Periodontal Res*. 2001;36(1):48-55.
2. Offenbacher S. Periodontal diseases: pathogenesis. *Ann Periodontol*. 1996;1(1):821-878.
3. Arbes SJ Jr, Slade GD, Beck JD. Association between extent of periodontal attachment loss and self-reported history of heart attack: an analysis of NHANES III data. *J Dent Res*. 1999;78(12):1777-1782.
4. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular disease. *J Cardiovasc Risk*. 1999;6(1):7-11.
5. Buhlin K, Gustafsson A, Håkansson J, et al. Oral health and cardiovascular disease in Sweden. *J Clin Periodontol*. 2002;29(3):254-259.
6. Angeli F, Verdecchia P, Pellegrino C, et al. Association between periodontal disease and left ventricle mass in essential hypertension. *Hypertension*. 2003;41(3):488-492.
7. Shimazaki Y, Saito T, Kiyohara Y, et al. Relationship between electrocardiographic abnormalities and periodontal disease: the Hisayama Study. *J Periodontol*. 2004;75(6):791-797.
8. Elter JR, Champagne CM, Offenbacher S, et al. Relationship of periodontal disease and tooth loss to prevalence of coronary heart disease. *J Periodontol*. 2004;75(6):782-290.
9. Buhlin K, Gustafsson A, Ahnve S, et al. Oral health in women with coronary heart disease. *J Periodontol*. 2005;76(4):544-550.
10. Wu T, Trevisan M, Genco RJ, et al. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Arch Intern Med*. 2000;160(18):2749-2755.
11. Joshipura KJ, Hung HC, Rimm EB, et al. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke*. 2003;34(1):47-52.
12. Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. *Stroke*. 2004;35(9):2020-2023.
13. Dörfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. *J Clin Periodontol*. 2004;31(5):396-401.
14. Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. *Stroke*. 2004;35(2):496-501.
15. Hujoel PP, Drangsholt M, Spiekerman C, et al. Periodontitis-systemic disease associations in the presence of smoking — causal or coincidental? *Periodontol 2000*. 2002;30:51-60.
16. Hujoel P. US Dept of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Periodontitis and cardiovascular diseases — Comorbid conditions? Feb 2005. Available at: http://www.cdc.gov/OralHealth/conferences/periodontal_infections06.htm. Accessed Nov 12, 2005.
17. Lowe GD. The relationship between infection, inflammation, and cardiovascular disease: An overview. *Ann Periodontol*. 2001;6(1):1-8.
18. De Nardin E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. *Ann*

Periodontol. 2001;6(1):30-40.
19. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis. Prospective results from a large population study. *Circulation*. 2001;103(8):1064-1070.
20. Buhlin K, Gustafsson A, Pockley AG, et al. Risk factors for cardiovascular disease in patients with periodontitis. *Eur Heart J*. 2003;24(23):2099-2107.
21. D'Aiuto F, Parkar M, Andreaou G, et al. Periodontitis and atherogenesis: causal association or simple coincidence? *J Clin Periodontol*. 2004;31(5):402-411.
22. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685-1695.
23. Ebersole JL, Machen RL, Steffen MJ, et al. Systemic acute-phase reactants, C-reactive protein and haptoglobin in adult periodontitis. *Clin Exp Immunol*. 1997;107(2):347-352.
24. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol*. 2001;72(9):1221-1227.
25. Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol*. 2003;23(7):1245-1249.
26. Slade GD, Ghezzi EM, Heiss G, et al. Relationship between periodontal disease and C-reactive protein among adults in the Atherosclerosis Risk in Communities study. *Arch Intern Med*. 2003:163(10):1172-1179.
27. Leivadaros E, van der Velden U, Bizzarro S, et al. A pilot study into measurements of markers of atherosclerosis in periodontitis. *J Periodontol*. 2005;76(1):121-128.
28. Di Napoli M, Papa F, Bocola V. Periodontal disease, C-reactive protein, and ischemic stroke. *Arch Intern Med*. 2001;161(9):1234-1235.
29. Haraszthy VI, Zambon JJ, Trevisan M, et al. Identification of periodontal pathogens in atheromatous plaques. *J Periodontol*. 2000;71(10):1554-1560.
30. Kesavalu L, Chandrasekar B, Ebersole JL. *In vivo* induction of proinflammatory cytokines in mouse tissue by *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*. *Oral Microbiol Immunol*. 2002;17(3):177-180.
31. Li L, Messas E, Batista EL, et al. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation*. 2002;105(7):861-867. Erratum in: *Circulation*. 2002;105(13):1617.
32. Jain A, Batista EL Jr, Serhan C, et al. Role for periodontitis in the progression of lipid deposition in an animal model. *Infect Immun*. 2003:71(10):6012-6018.
33. Miyakawa H, Honma K, Qi M, et al. Interaction of *Porphyromonas gingivalis* with low-density lipoproteins: implications for a role for periodontitis in atherosclerosis. *J Periodontal Res*. 2004;39(1):1-9.
34. Qi M, Miyakawa H, Kuramitsu HK. *Porphyromonas gingivalis* induces murine macrophage foam-cell formation. *Microb Pathog*. 2003;35(6):259-267.
35. Lalla E, Lamster IB, Hofmann MA, et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. *Arterioscler Thromb Vasc Biol*. 2003;23(8):1405-1411.
36. Gibson FC 3rd, Hong C, Chou HH, et al. Innate immune recognition of invasive bacteria accelerates atherosclerosis in apolipoprotein E-deficient mice. *Circulation*. 2004;109(22):2801-2806.
37. Pussinen PJ, Jousilahti P, Alfthan G, et al. Antibodies to periodontal pathogens are associated with coronary heart disease. *Arterioscler Thromb Vasc Biol*. 2003;23(7):1250-1254.
38. Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. *Stroke*. 2004;35(9);2020-2023.
39. Kuramitsu HK, Kang IC, Qi M. Interactions of *Porphyromonas gingivalis* with host cells: Implications for cardiovascular diseases. *J Periodontol*. 2003;74(1):85-89.
40. Kuramitsu HK, Qi M, Kang IC, et al. Role for periodontal bacteria in cardiovascular diseases. *Ann Periodontol*. 2001;6(1):41-47.
41. Yamazaki K, Ohsawa Y, Tabeta K, et al. Accumulation of human heat shock protein 60-reactive T cells in the gingival tissues of periodontitis patients. *Infect Immun*. 2002;70(5):2492-2501.
42. Yamazaki K, Ohsawa Y, Itoh H, et al. T-cell clonality to *Porphyromonas gingivalis* and human heat shock protein 60s in patients with atherosclerosis and periodontitis. *Oral Microbiol Immunol*. 2004;19(3):160-167.
43. Chung SW, Kang HS, Park HR, et al. Immune responses to heat shock protein in *Porphyromonas gingivalis*-infected periodontitis and atherosclerosis patients. *J Periodontal Res*. 2003;38(4):388-393.
44. Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima-media thickness. The Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation*. 2005;111(5):576-582.
45. Kozarov EV, Dorn BR, Shelburne CE, et al. Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Arterioscler Thromb Vasc Biol*. 2005;25:e17-e18.
46. Marques da Silva R, Caugant DA, Lingaas PS, et al. Detection of *Actinobacillus actinomycetemcomitans* but not bacteria of the red complex in aortic aneurysms by multiplex polymerase chain reaction. *J Periodontol*. 2005;76(4):590-594.
47. Marques da Silva R, Lingaas PS, Geiran O, et al. Multiple bacteria in aortic aneurysms. *J Vasc Surg*. 2003;38:1384-1389.
48. Fiehn NE, Larsen T, Christiansen N, et al. Identification of periodontal pathogens in atherosclerotic vessels. *J Periodontol*. 2005;76(5):731-736.
49. Dögan B, Buduneli E, Emingil G, et al. Characteristics of periodontal microflora in acute myocardial infarction. *J Periodontol*. 2005;76(5):740-748.
50. Syrjänen J, Peltola J, Valtonen V, et al. Dental infections in association with cerebral infarction in young and middle-aged men. *J Intern Med*. 1989;225(3):179-184.
51. Mattila KJ, Nieminen MS, Valtonen VV, et al. Association between dental health and acute myocardial infarction. *BMJ*. 1989;298(6676):779-781.
52. Beck J, Garcia R, Heiss G, et al. Periodontal disease and cardiovascular disease. *J Periodontol*. 1996;67(10 Suppl):1123-1137.
53. DeStefano F, Anda RF, Kahn HS, et al. Dental disease and risk of coronary heart disease and mortality. *BMJ*. 1993;306(6879):688-691.
54. Buhlin K, Gustafsson A, Ahnve S, et al. Oral health in women with coronary heart disease. *J Periodontol*. 2005;76(4):544-550.
55. Nakib SA, Pankow JS, Beck JD, et al. Periodontitis and coronary artery calcification: the Atherosclerosis Risk in Communities (ARIC) study. *J Periodontol*. 2004;75(4):505-510.
56. Beck JD, Elter JR, Heiss G, et al. Relationship of periodontal disease to carotid artery intima-media wall thickness: the Atherosclerosis Risk in Communities (ARIC) study. *Arteioscler Thromb Vasc Biol*. 2001;21(11):1816-1822.

57. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on progression of carotid atherosclerosis. *Stroke*. 2002;33(11):2581-2586.
58. Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: the Oral Infections and Vascular Disease Epidemiology study (INVEST). *Stroke*. 2003;34(9):2120-2125.
59. Elter JR, Offenbacher S, Toole JF, et al. Relationship of periodontal disease and edentulism to stroke/TIA. *J Dent Res*. 2003;82(12):998-1001.
60. Dörfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. *J Clin Periodontol*. 2004;31(5):396-401.
61. Epstein SE, Zhu J, Burnett MS, et al. Infection and atherosclerosis: potential roles of pathogen burden and molecular mimicry. *Arterioscler Thromb Vasc Biol*. 2000;20(6):1417-1420.
62. Zhu J, Quyyumi AA, Norman JE, et al. Effects of total pathogen burden on coronary artery disease risk and C-reactive protein levels. *Am J Cardiol*. 2000;85(2):140-146.
63. Zhu J, Nieto J, Horne BD, et al. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation*. 2001;103(1):45-51.
64. Iwamoto Y, Nishimura F, Soga Y, et al. Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-alpha, but not adiponectin levels in patients with chronic periodontitis. *J Periodontol*. 2003;74(8):1231-1236.
65. D'Aiuto F, Parkar M, Andreou G, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res*. 2004;83(2):156-160.
66. D'Aiuto F, Nibali L, Parkar M, et al. Short-term effects of intensive periodontal therapy on serum inflammatory markers and cholesterol. *J Dent Res*. 2005;84(3):269-273.

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THE SIGNIFICANCE OF PERIODONTAL INFECTION IN CARDIOLOGY

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Abstract
Molecular and cellular biology and the physiologic mechanisms of disease constitute the basis of treatment in both cardiology and periodontics. Recognizing inflammation as the common denominator in the pathobiology of cardiovascular and periodontal disease provides an excellent opportunity for dental and medical professionals to collaborate on decreasing patients' risk for cardiovascular disease (CVD), or its progression. This article focuses on empowering dental and medical professionals to incorporate the latest evidence on the relationship of periodontal and cardiovascular disease by presenting an in-depth view of the inflammatory process involved with atherosclerosis. Further, this article will discuss the significance of infections such as periodontal disease in increasing the systemic inflammatory burden and risk for atherosclerosis and, thereby, increasing the risk for CVD. In addition, a rationale for why periodontal disease should be considered a risk correlate of CVD is presented. Also discussed is the use of the Framingham CVD risk assessment instrument and high-sensitivity C-reactive protein (hsCRP) testing in dental practices and screening for periodontal disease in medical practices. This article concludes by challenging readers to realize the undeniable therapeutic opportunity of medical-dental collaboration in reversing the rather somber trends in CVD.

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Key words: Periodontitis, cardiovascular disease, bacteria, inflammation, risk factors

Most of us have heard the refrain from an old song, "The ankle bone is connected to the leg bone." Can we now sing, "The gums are connected to the heart?" As unlikely as this may sound, researchers and clinicians may have ample evidence to support this claim. Pilot intervention studies are now underway, but should we wait for those final answers before we consider periodontal disease as a risk correlate for CVD? And, if we move ahead now, how do health-care providers implement the current evidence?

Cardiologists and dental professionals appear to have a common enemy — chronic inflammation and its potential to accelerate the process of atherosclerosis, a widely recognized prelude to cardiovascular diseases. Science is beginning to reveal that destructive inflammatory periodontal diseases release substances that are involved in arterial wall inflammation, development of atherosclerosis, and rupture of established atheromas which result in myocardial infarction (MI) and stroke.[1,2] It is the atherosclerotic lesion that amplifies the risk for CVD.

Is human atherosclerosis an inevitability of aging? The hypothesis that human atherosclerosis is not an absolute consequence of aging and can be reversed was put forth in the 1980s by Malinow's pioneering work aimed at halting the progression of atherosclerosis and promoting its regression.[3,4] Mounting evidence appears to strengthen Malinow's hypothesis that old age may not necessarily equate to atherosclerosis. A recent study of more than 1,000 participants with a mean age of 73 found that for older adults, periodontal disease, which is one of the infections implicated as a cause of endothelial injury leading to atherosclerosis, is a modifiable risk indicator for elevated levels of systemic

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inflammatory markers, including interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and hsCRP.[5] All three of these markers are widely recognized as being associated with periodontal infection.[6-8] The question becomes, "Could treatment of periodontal disease in patients both at an earlier stage and age translate into greater longevity?"

Challenges in Decreasing the Incidence and Severity of CVD —

More than 20 years have passed since Malinow tackled CVD. With an array of therapeutic strategies at hand, many health-care providers hoped that CVD would be eliminated by the end of the 20th century. At the beginning of the 21st century, despite cardiologists' recommendations to patients for therapeutic lifestyle changes targeting classic risk factors — a diet restricted in calories to reach a body mass index of <25 kg/m^2; a waist circumference <105 cm in men and <90 cm in women; physical exercise, smoking cessation, and blood pressure control; and the widespread use of statins in treating hypercholesterolemia — CVD still accounts for 38% of all deaths in North America.[2] Largely because of its rapidly increasing prevalence in Eastern Europe and developing countries, and the obesity trends and rising incidence of diabetes in the West, coronary heart disease (CHD) is expected to be the main cause of death globally.[9] However, about half of patients presenting with MI do not have classic risk factors for CVD.[10] CVD was once thought of as a disease primarily induced by accumulation of lipid-laden cells. What we now know is that high cholesterol is important in only 50% of patients with coronary artery disease (CAD).[1] "Even with intensive statin therapy, the best current evidence-based treatment available, many patients will still have recurrent cardiovascular events."[11] Although statin therapies have been successful for a large segment of the population, it appears that the medical community may need to pursue approaches beyond statins to modify the course of vascular diseases.[11]

Hardly daunted by the most progressive disease-management strategies, the prediction, prevention, and treatment of CVD represents one of the greatest challenges facing all of us in the health-care arena. This dismal revelation begs an important question: "If we are to implement the recommendations made by the Surgeon General in the *Oral Health in America* report,[12] already five years old, and achieve the target goals set by the Centers for Disease Control and Prevention,[13] should we include in risk assessments for CVD those factors associated but that, at present, are not proven to be causative, independent, or quantitative?

The answer may be "yes," but this level of comprehensive care will require medical and dental professionals who are willing to champion this message and initiate models of collaborative care. The intervention trials necessary to prove a cause-and-effect relationship between periodontal disease and CVD are currently underway or about to be funded. Accumulation of that evidence will take years. In the meantime, do we not have enough evidence to support periodontal disease at least as a risk correlate for CVD?

The prevalence of both periodontitis and atherosclerosis is rampant. Periodontal disease is a "preventable [and treatable] contributor to the burden of cardiovascular disease,"[14] and as such, is a modifiable risk factor — a fact that may be escaping the attention of both medical and dental professionals. If only a marginal association between these two diseases is found, prevention and treatment of periodontal disease may have an impact on the prevalence of CVD. It is not premature to include periodontal disease as a risk correlate for CVD, and failure to do so may forfeit an important therapeutic opportunity to reduce or eliminate a modifiable risk factor for CVD.

Quantifying Risk for CVD —

Table 1 on page 26 classifies various risk factors according to their quantitative association with CVD as elucidated by the Framingham Heart Study, which estimates risk for people without clinical manifestations of CVD. Scores derived from the Framingham risk assessment only apply to the primary prevention of CVD.[15] Once coronary atherosclerosis is clinically manifested, the risk for future coronary events is much higher than that for patients without CVD, regardless of other risk factors.[15] Therefore, the Framingham scores no longer apply.[15]

When considering the various risk factors for CHD (Table 1), it is important to understand that major risk factors are additive in predictive power in that total risk can be estimated by the summation of the individual risks related to each factor.[15] However, the major risk factors for CVD as identified in Table 1 do not account for all the variations in the incidence and severity of CVD. Accordingly, it is important to point out that other, less well documented risk factors for CVD may play a significant role.[16]

A strong argument may be made that periodontal disease should be considered both a predisposing and a conditional

Table 1
Factors Associated With Increased Risk for CVD.[15] *(Correlated to the Framingham Heart Study.)*
Should periodontal disease be added to this list?

Major Independent Risk Factors
- Advancing age
- Cigarette smoking
- Diabetes
- Elevated blood pressure
- Elevated serum total (and LDL) cholesterol
- Low serum HDL cholesterol

Predisposing Risk Factors
- Abdominal obesity§
- Ethnic characteristics
- Family history of premature coronary heart disease
- Obesity†§
- Physical inactivity†
- Psychosocial risk factors

Periodontal disease?

Conditional risk factors
- Elevated serum homocysteine
- Elevated serum lipoprotein (a)
- Elevated serum triglycerides
- Inflammatory markers (e.g. C-reactive protein)
- Prothrombotic factors (e.g. fibrinogen)
- Small LDL particles

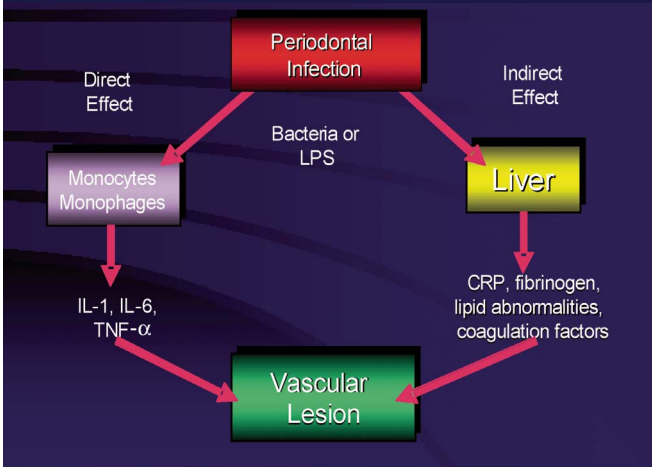
† These risk factors are defined as major risk factors by the American Heart Association
§ Body weights are currently defined according to BMI as follows: normal weight 18.5 kg/m² to 24.9 kg/m²; overweight 25 kg/m²to 29 kg/m²; obesity >30.0 kg/m²; (obesity class I 30.0 kg/m²to 34.9 kg/m²; class II 35.9 kg/m²to 39.9 kg/m², class III ≥50 kg/m²). Abdominal obesity is defined according to waist circumference: men >102 cm (>40") and women >88 cm (>35").

risk factor for CVD. Predisposing risk factors are agents that worsen independent risk factors.[15] The bidirectional relationship between periodontal disease and diabetes would seem to qualify periodontal disease as a predisposing risk factor for diabetic complications.[17-21] Conditional risk factors are associated with an increased risk for CVD, although their causative contributions to CVD have not been well documented.[15] Such is the case for the correlation between periodontal disease and increased risk for atherosclerosis. The presence of predisposing and conditional risk factors in the assessment of risk for CVD may confer greater risk than revealed from the summation of the major risk factors.[15] Although their contribution has not been quantified, this does not mean that they do not make an independent contribution to risk when they are present.[15] Accordingly, what may be left off this list of risk factors in Table 1 is the contribution of periodontal infection in accelerating atherosclerosis eventuating in CVD.

During the last 20 years there has been significant progress in understanding the link between periodontal infections and risk for CVD such as heart disease[22], stroke, and peripheral vasculature disease, all of which share atherosclerosis as a common feature.[16,23] Recent research found bacterial levels were elevated in only those patients with a history of myocardial infarction, suggesting that increased loads of subgingival bacteria present a danger for systemic health.[24]

The growing research to support the contribution of periodontal infection to the inflammatory burden is theorized to be through both a direct action on blood vessel walls, and by indirectly inducing the liver to produce

Figure 1¥ — Model for systemic spread of periodontal infection and effects on the vasculature



acute phase proteins (e.g., CRP) (Figure 1).[25] Until recently, DNA footprints comprised the bulk of evidence suggesting that periodontal bacteria were directly involved in atherosclerosis. However, research at the University of Florida has demonstrated that *Porphyromonas gingivalis (P. gingivalis)* and *Actinobacillus actinomycetemcomitans (A. actinomycetemcomitans)* are capable of adapting to the vasculature to live in human atherosclerotic lesions.[26] On the medical side, a study recently reported in the *American Heart Journal* found that periodontal disease is common in patients with MI and associated with elevated

¥ Reprinted from *Periodontics: Medicine, Surgery, and Implants*, Rose LF, Mealey BL, Genco RJ, Cohen DW, pg 848, Copyright 2004, with permission from Elsevier.

hsCRP levels typical of an enhanced systemic inflammatory response.[27] These associations were found to be independent of other contributing factors.[27] Other studies indicate an association between periodontal disease and elevated hsCRP and IL-6, and, conversely, that periodontal treatment lowered hsCRP and IL-6 with a simultaneous improvement in endothelial function.[28] As compelling as this research may be, the truth is that the evidence only supports, but does not prove, a causal association between periodontal disease and atherosclerosis-related diseases. Until this etiological mystery is decoded, we are faced with the dilemma of how to implement treatment strategies that are supported by the existing body of evidence.

Although a combination of risk factors may contribute to the progression of an atherosclerotic lesion, researchers now consider infection to be a significant inflammatory stimulus.[28] Inflammation is directly implicated in destabilization of atherosclerotic plaque in the carotid artery[1] and may lead to aneurism and embolism.[1] Seeding of live periodontal bacteria from the oral cavity to vessel walls,[26] a hyperinflammatory response to those periodontal pathogens,[29] and activation of proinflammatory mediators are three biological mechanisms implicated in the induction of a systemic inflammatory response.[26] This chain of events may describe the link between periodontal disease and CVD.

To fully understand the significance of periodontal disease in the cascade of events implicated in the formation of an atherosclerotic lesion, it is important that dental practitioners understand that infection is a well-established risk factor for atheroma formation and thromboembolic events.[16] To that end, discussion and illustration of the role of infection in the developing atherosclerotic lesion may help readers gain a more comprehensive understanding of this cascade of pathological events.

The Contribution of Infection in the Developing Atherosclerotic Lesion —

It is known that atherosclerosis is the main cause of CVD.[1,2] Possible causes of the endothelial dysfunction that lead to atherosclerosis include elevated and modified low density lipoprotein (LDL); free radicals caused by cigarette smoking; hypertension and diabetes; genetic alterations; and elevated plasma homocysteine concentrations.[1] Most germane are the studies that have also linked infection to atherosclerotic-induced diseases. What has become apparent is that several types of microbial pathogens may contribute to atherosclerosis, making it highly unlikely that a single microbe causes atherosclerosis.[2] It is now thought that the cumulative burden of infection at various sites is what affects the progression of atherosclerosis and its clinical manifestations of CVD.[2]

There are many studies to support the specific correlation of periodontal infection and atherosclerosis, and a few more recent pieces of evidence merit mention. Various studies have implicated *P. gingivalis*, a virulent periodontal pathogen, as part of a transient bacteremia that can lead to the direct invasion of blood vessels.[30] In addition, *P. gingivalis* is implicated in several steps involved in the formation of the atherosclerotic lesion.[31,32] In 2003, it was reported that subjects with advanced periodontal disease exhibited endothelial dysfunction and evidence of systemic inflammation (elevated serum CRP levels), placing them at increased risk for CVD.[33] More recently, there is serological evidence that an infection caused by *P. gingivalis* increases the risk for MI; high *P. gingivalis* antibody levels have been shown to predict MI independently of classical cardiovascular risk factors,[34] and infection caused by major periodontal pathogens may be associated with future stroke.[35] Periodontal disease was found to be a treatable, independent risk factor for cerebral ischemia in male subjects (<60 years of age). Those with severe periodontitis had a 4.3 times greater risk of cerebral ischemia than subjects with mild periodontitis or healthy subjects.[36] Gingivitis and severe radiological bone loss were also independently associated with the risk of cerebral ischemia while tooth decay was not.[36]

A recent investigation demonstrated a direct relationship between microorganisms from periodontal infection and subclinical (undetected) atherosclerosis.[37] This relationship was found to be independent of hsCRP.[37] The same research found that bacteria causally related to periodontitis are related to increased carotid intima-media thickness (IMT),[37] an important marker of early atherosclerosis. This was true even after adjusting for conventional risk factors (i.e., age, race/ethnicity, body mass index (BMI), smoking, diabetes, systolic blood pressure, LDL, and high-density lipoprotein [HDL] cholesterol),[37] providing even more evidence of a direct role of certain infections in the pathogenesis of atherosclerosis. The same study found that white blood cell values tend to rise with both increasing levels of periodontopathic bacteria and increased carotid IMT.[37] Similar research findings continue to accumulate, strengthening the evidence that inflammation, either direct or from a distance (as in periodontal disease) is a primary etiology for affecting alterations in endothelial function which, left untreated, eventually develops into an

atherosclerotic lesion.

An atheroma forms in the arterial wall as a result of inflammation.[1] The atheroma is made up of smooth muscle proliferation in the media of the arterial wall.[1] Other inflammatory changes in the media are seen distorting the anatomy of the arterial wall.[1] This is covered by a fibrous cap on the luminal surface narrowing the lumen to a greater or lesser extent, depending on the circumstances.[38] Some feel that distortion is more dangerous than luminal stenosis.[38] Over time, the fibrous cap thins and ruptures with matrix metalloproteinases (MMPs) playing a role in the degradation of the collagen within the fibrous cap.[38] This presents a rough surface to flowing blood in the lumen.[38] Platelets adhere to this surface under the influence of adhesion factor activity, causing a coagulation cascade leading to an occluding clot, cutting off all blood flow.[38] This results in stroke or MI, depending on the location.[38]

Ross wrote a 1999 review article in the *New England Journal of Medicine* titled "Atherosclerosis — An Inflammatory Disease," which is used in teaching institutions to provide a step-by-step description of the development of the atherosclerotic lesion.[1] In this review, Ross detailed the atherosclerotic process beginning with endothelial dysfunction, the formation of the fatty streak, and then the formation of the advanced complicated atherosclerotic lesion, ending with how unstable fibrous plaque can rapidly lead to thrombosis. Illustrations and accompanying explanations of the contribution of infection in the atherosclerotic process are provided in Figures 2 to 5 on page 29 to help readers better understand the pathobiological cascade of events implicated in the formation of an atherosclerotic lesion.

Making the Case for hsCRP Testing in Dental Practices —
It is becoming increasingly clear that the variety of cardiovascular events cannot be explained by a single pathobiological pathway. The relationship between novel biological markers of inflammation and traditional risk factors, such as high blood pressure, smoking, obesity, diabetes, low levels of physical activity, and use of hormone-replacement therapy, may be of variable importance for individual patients.[39] This has spawned a search for other factors that may be implicated and, when present, help to identify patients at greater risk for MI and other cardiovascular events.[10] Certain markers of inflammation (systemic and local) appear to play a central role in the development and progression of atherosclerosis.[10] HsCRP, one of the acute-phase proteins produced by the liver in response to infection, is a specific systemic marker of vascular inflammation that appears to have a strong association with adverse vascular events.[39]

Both hsCRP and LDL cholesterol levels are elevated in people at risk for cardiovascular events. However, hsCRP and LDL cholesterol measurements tend to identify different high-risk groups.[39] Researchers have found that independent effects were observed for hsCRP in analyses adjusted for all components of the Framingham risk score[39] (i.e., traditional risk factors for CVD). Specifically, hsCRP and LDL cholesterol levels are minimally correlated and hsCRP has been found to be a stronger predictor of future cardiovascular events than LDL cholesterol.[39] This advantage persisted after adjusting for all traditional cardiovascular risk factors and included the effect of hormone-replacement therapy at baseline.[39] The researchers further concluded that the combined evaluation of both hsCRP and LDL cholesterol proved to be a superior method of detecting risk for cardiovascular events than measurement of either biological marker alone.[39]

What is the normal range of hsCRP level? [40]

- If hsCRP level is lower than 1.0 mg/L, a person has a low risk of developing cardiovascular disease.
- If hsCRP is between 1.0 mg/L and 3.0 mg/L, a person has an average risk.
- If hsCRP is higher than 3.0 mg/L, a person is at high risk.

Low-grade chronic inflammation as measured by hsCRP predicts future risk of acute coronary syndromes independent of traditional cardiovascular risk factors.[41] Because periodontal infection appears to be a source of low-grade chronic infection, the use of hsCRP testing in dental practices provides an excellent opportunity for identifying patients at risk for acute coronary syndromes.

The Role of Dental Professionals in Screening Patients for CVD Risk —
Along with monitoring blood pressure, which has long been routine in practice, the addition of chairside hsCRP testing in dental practices has the potential to become a significant tool for identification of patients at risk for CVD. This may be especially valuable in primary prevention of CVD. Current research considers subclinical (undetected) inflammation to be an accelerant of vascular inflammation and markers of inflammation (both systemic and local), which, in turn, appear to play a central role in the development and progression of atherosclerosis.[10] Indeed, many patients seen by health-care professionals are at

Figures 2 — 5: Evolution of the atherosclerotic lesion

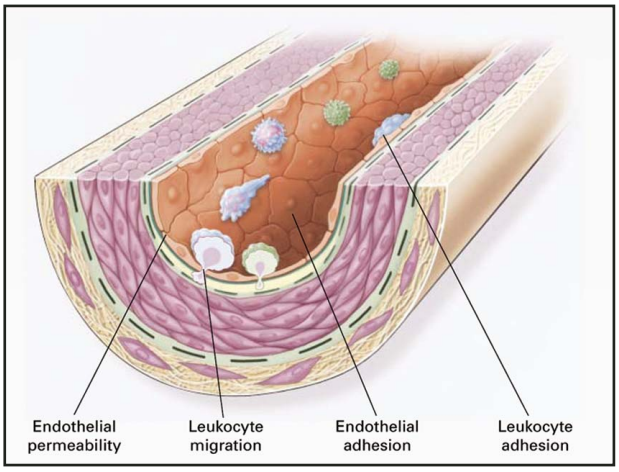


Figure 2 — Endothelial dysfunction in atheroslerosis.[1]
The earliest changes preceding the formation of atherosclerotic lesions involve the endothelial lining of the vessel lumen. The changes include increased endothelial permeability that leads to acculumation of lipoproteins and development of the fatty streak; up-regulation of endothelial adhesion molecules that facilitate the aggregation of monocytes, T-lymphocytes, and blood platelets; and endothelial/platelet interactions resulting in the release of growth factors that, in turn, promote progressive development of the lesion.

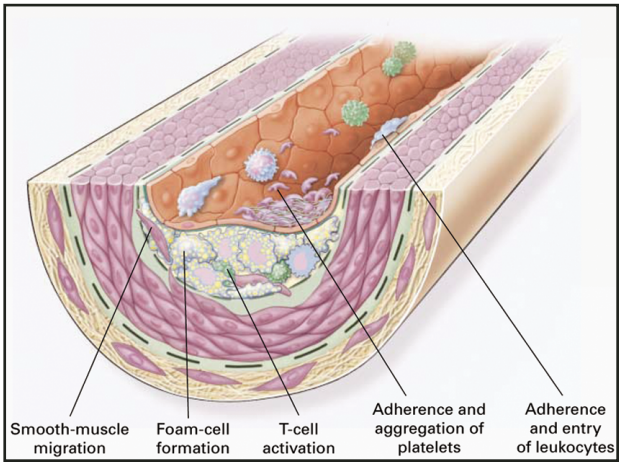


Figure 3 — Fatty-streak formation in atherosclerosis.[1]
Fatty streaks initially consist of lipid-laden monocytes and macrophages (foam cells) together with T-lymphocytes. Later, they are joined by increasing numbers of smooth muscle cells, some of which may also contain varying amounts of lipid. The increasing population of smooth muscle cells is promoted by various growth factors, such as Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and Transforming Growth Factor-ß (TGF-ß).

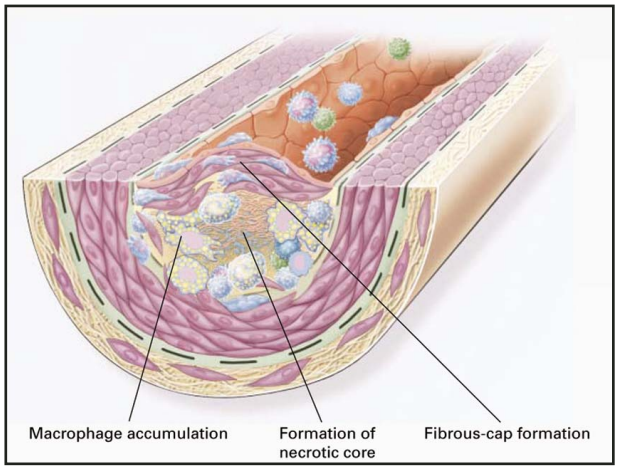


Figure 4 — Formation of an advanced, complicated lesion of atherosclerosis.[1]
Intermediate and advanced atherosclerotic lesions are characterized by a fatty streak covered by a fibrous connective tissue cap. The cap represents a healing response to injury and forms a barrier between the underlying lesion and the vessel lumen. The fibrous connective tissue layer is infiltrated by lipid-filled macrophages and smooth muscle cells, all of which cover a mixture of leukocytes, extracellular lipids, and debris that, in turn, may form a necrotic core.

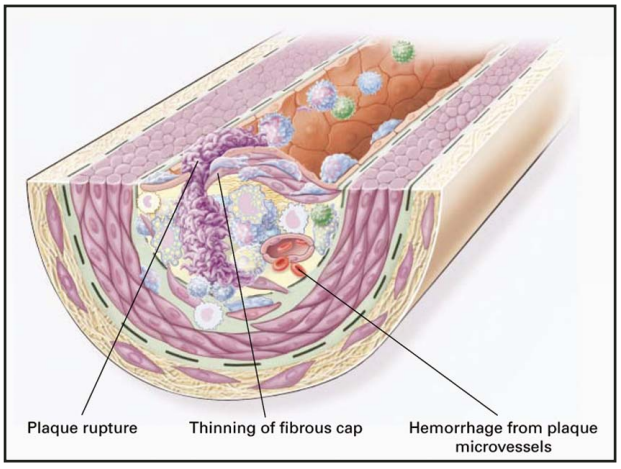


Figure 5 — Unstable fibrous plaques in atherosclerosis.[1]
Rupture or ulceration of the fibrous cap can lead to hemorrhage and thrombosis and usually occurs at sites where the connective tissue layer is thin. Thinning of the fibrous cap is apparently because of the continuing influx and activation of macrophages, which release metalloproteinases and other proteolytic enzymes. The enzymes degrade collagen and noncollagenous matrix proteins, which then leads to hemorrhage, thrombus formation, and occlusion of the vessel. In some cases, an embolus of clotted blood may be released and occlude a downstream vessel.

Medical illustrations used with permission from the *New England Journal of Medicine*

increased risk for MI or stroke because of undiagnosed and asymptomatic atherosclerosis which may be accelerated by chronic periodontal infection.

In 2002, the Centers for Disease Control and Prevention and the American Heart Association held a conference to examine (among other things) the selection and use of inflammatory markers to predict CVD risk. Recommendations made at the conference which have specific relevance to the present discussion follow:[42]

1) *Of all the inflammatory markers identified, hsCRP, as an independent marker of risk, may be used at the discretion of the physician as part of an office-based global risk assessment (i.e., the Framingham Heart Study) in adults without known CVD. HsCRP may identify those patients for further intervention or therapy in the primary prevention of CVD.*[42]

Dental professionals also are well-positioned to assist patients in assessing their global risk for CVD through use of an assessment such as the Framingham instrument.

2) *Testing for hsCRP provides an additive element to global risk assessment. As a result, patients without known CVD who were not previously considered to be at risk will be identified and targets for more aggressive risk reduction interventions. It was recommended that hsCRP be measured in patients who are at intermediate risk of CHD per 10 years (as indicated in global risk assessment) to direct further evaluation and therapy in the primary prevention of CVD.*[42]

A good example of this would be a patient who has been identified by a dental professional as being at intermediate risk of CVD via global risk assessment such as the Framingham risk assessment. For example, if a person's cardiovascular risk score — judged by global risk assessment — is low (the possibility of developing CVD is <10% in 10 years), hsCRP testing is not immediately warranted.[39] If the risk score is in the intermediate range (10% to 20% in 10 years), such a test can help predict a cardiovascular and stroke event and help direct further evaluation and therapy.[39] However, the benefits of such therapy based on this strategy remain uncertain.[39] If a dental professional intercepts a person with a high risk score (>20% in 10 years) or established heart disease or stroke, this is an individual who should receive intensive medical care regardless of hsCRP levels[38] and should be triaged to the care of a cardiologist as soon as possible.

3) *It was recommended that patients with persistently unexplained marked elevation of hsCRP (>10 mg/L) after repeated testing should be evaluated for noncardiovascular causes, such as infection and inflammation.*[42]

These are the types of patients cardiologists should refer to periodontists to be examined for periodontal disease.

4) *It was suggested that detection of an elevated hsCRP might serve to motivate patients to adhere to better preventive therapies.*[42]

This might be the case for a prediabetic patient whose hsCRP is tested by a dental hygienist chairside and discovered to be edging toward "high normal" (2 mg/L to 10 mg/L), which is predictive of heart disease. In this situation, a dental hygienist has a valuable role to play in motivating that patient to adhere to proper diet, physical fitness programs, compliance to medication regimens, or, possibly, smoking cessation counseling.

Testing for hsCRP in Dental Practices

Is it time for dental professionals to screen patients for risk of future cardiovascular events by performing chairside testing for hsCRP? Yes, and those technologies are now entering the health-care market.

The cardiologist who co-authored this article frequently asks new patients who have heart disease or who are at high risk for heart disease when they last saw their dentists, and whether they were examined for periodontal disease. He also visually examines the gingival tissue and general conditions of the teeth. An example of collaborative care involves a young, non-obese female patient with an elevated hsCRP, but normal serum lipids and blood pressure, who presented with severe gingival inflammation. The cardiologist referred this patient to a periodontist. Four months later, following periodontal therapy, her hsCRP was normal.

The cardioprotective benefits of periodontal treatment may represent an efficacious modification to contemporary therapies for vascular diseases. Several pilot studies have shown that periodontal therapy consisting of scaling and root planing and application of antimicrobial agents were effective in reducing levels of serum inflammatory markers, specifically hsCRP, IL-6, and TNF-α.[43,44] However, larger scale, randomized interventional clinical trials are needed to investigate the potential cardiovascular benefits

of periodontal therapy.[7] If future research provides evidence that treatment of periodontitis reduces hsCRP and/or decreases the incidence of CVD, this would provide a strong rationale for a change in health-care policy that would position periodontal care as medically necessary for the prevention and management of CVD.[7] In the meantime, it is time for physicians and other nondental health-care providers to begin to identify those patients who are at greater risk for periodontal disease because of their individual risk profiles. Specifically, patients who smoke are at 3 to 7 times greater risk and patients with diabetes are at 2 to 5 times greater risk for developing periodontal disease.[45] Patients who report that a sibling or parent lost their teeth at an early age may be genetically predisposed to periodontal disease with an odds ratio that confers 3 to 5 times greater risk for developing periodontal disease.[45] Those patients who both smoke and who are genotype positive have an 8 to 10 times greater risk for periodontal disease.[45] These scenarios represent excellent opportunities for the medical community to screen for periodontal disease and triage patients to dental professionals for evaluation and treatment of periodontal disease.

Discussion of the significance of periodontal infection in cardiology would be incomplete without mentioning the potential role subantimicrobial doses of doxycycline may play in inhibiting MMPs. MMPs participate in degradation of the fibrous cap of an atherosclerotic lesion (the vulnerable plaque), which ultimately leads to rupture, in-situ thrombosis, and subsequent vascular events.[46] Although larger studies are needed to investigate its potential to reduce the risk of rupture of atherosclerotic plaque, it appears that subantimicrobial doses of doxycycline, approved by the U.S. Food and Drug Administration for suppression of collagen-destroying enzymes in the treatment of periodontal disease, may also have cardioprotective benefits.[46]

Conclusion

Despite the fact that the formation of the atherosclerotic lesion and its impending threat to cardiovascular health has a very complex etiology, dental screening to identify patients at risk for CVD and those patients with diagnosed CVD who are at greater risk for recurrent cardiovascular events offers an undeniable intervention opportunity. Likewise, physicians have an enormous part to play by screening patients for periodontal disease.

For patients at intermediate risk (10% to 20% risk of CHD per 10 years) as defined by the Framingham risk score, testing for hsCRP may help direct further evaluation and therapy in primary prevention for CVD.[47] For patients with stable coronary disease and acute coronary syndromes, in-office testing in dental practices for hsCRP may prove to be invaluable in identifying those patients who require significantly more aggressive therapies provided by cardiologists.

Although the cardioprotective benefits of periodontal treatment remain speculative at present, awareness of the relationship between the increased burden of infectious agents and systemic inflammation may have a significant effect on the prevention and treatment of chronic inflammatory diseases and conditions. Transition toward interdisciplinary health-care management must increase to better target those at high risk and to devise a multidisciplinary integrated care pathway for CVD. Those physicians and dentists who collaborate on this integrated care pathway will be ahead of the curve.

It is not unusual to hear from physicians that they have seen patients with hyperparathyroidism, diabetes, osteoporosis, and various other diseases that were first diagnosed in the dental office. Indeed, astute dentists and dental hygienists are often the first to note an undesirable side effect of calcium channel blockers (i.e. drug-induced gingival overgrowth). Many within the medical profession also recognize the significant contributions of many dental professionals in monitoring patients' blood pressure. It is important to realize that we are now in an unprecedented era of explosion of research related to periodontal medicine. For the well-being of our patients, the time has come for physicians, dentists, nurses, and dental hygienists to work together to identify those at risk, both for atherosclerosis and periodontal disease. Indeed, we are all treating "a patient," not just one part or one organ.

It is interesting that the oldest medical school in the world, the University of Bologna in Bologna, Italy (founded in 1088), still requires all medical students to take a one-year course in oral medicine and dentistry. Nine hundred seventeen years later, all physicians and dentists must realize that we treat an organism. The mouth is attached to the body and each may have an effect on the health of the other. We must remember the ankle bone is connected to the leg bone and, indeed, the oral cavity is connected to the body.

References

1. Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med.* 1999;340(2):115-126.
2. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* 2005;352(16):1685-1695.
3. Malinow MR. Atherosclerosis. Regression in nonhuman primates. *Circ Res.* 1980;46(3):311-320.
4. Malinow MR. Atherosclerosis. Progression, regression, and resolution. *Am Heart J.* 1984;108(6):1523-1537.
5. Bretz WA, Weyant RJ, Corby PM, et al. Systemic inflammatory markers, periodontal diseases, and periodontal infections in an elderly population. *J Am Geriatr Soc.* 2005 Sep;53(9):1532-1537.
6. The Research, Science, and Therapy Committee of the American Academy of Periodontology. The pathogenesis of periodontal diseases. *J Periodontol*. 1999;70(4);457-470.
7. American Academy of Periodontology coordination meeting on oral health and systemic health. Periodontal medicine: health policy implications. Geneva, Switzerland, December 5 and 6, 2002. *J Periodontol.* 2003;74(7):1080-1095.
8. Noack B, Genco RL, Trevisan M, et al. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol.* 2001;72(9):1221-1227.
9. World Health Organization. *The Atlas of Heart Disease and Stroke*. 2005. Available at: http://www.who.int/cardiovascular_diseases/resources/atlas/en/. Accessed Dec 11, 2005.
10. Koenig W. C-reactive protein: risk assessment in the primary prevention of atherosclerotic disease. Has the time come for including it in the risk profile? *Ital Heart J*. 2001;2(3):157-163.
11. Cannon CP. The ideal cholesterol. *JAMA*. 2005;294(19):2492-2494.
12. Satcher D. US Department of Health and Human Services. *Oral Health in America: A Report of the Surgeon General*. May 2000. Available at: http://www.surgeongeneral.gov/library/oralhealth. Accessed Nov 18, 2005.
13. US Department of Health and Human Services, Public Health Service. Healthy People 2010 Progress Review-Heart Disease and Stroke. Available at: www.healthypeople.gov/data/2010prog/focus12. Accessed April 15, 2005.
14. Beck JD, Elter JR, Heiss G, et al. Relationship of periodontal disease to carotid artery intima-media wall thickness: The atherosclerosis risk in communities study. *Atheroscler, Thromb, and Vasc Biology.* 2001;21(11):1816-1822.
15. Grundy SM, Pasternak R, Greenland P, et al. AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for health-care professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol*. 1999;34(4):1348-1359.
16. Jin LJ, Chiu GK, Corbet EF. Are periodontal diseases risk factors for certain systemic disorders—what matters to medical practitioners? *Hong Kong Med J*. 2003;9(1):31-37.
17. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. *Ann Periodontol.* 1998;3(1):51-61.
18. Nishimura F, Takahashi K, Kurihara M, et al. Periodontal disease as a complication of diabetes mellitus. *Ann Periodontol*. 1998;3(1):20-29.
19. Schmidt AM, Weidman E, Lalla E, et al. Advanced glycation endproducts (AGEs) induce oxidant stress in the gingiva: a potential mechanism underlying accelerated periodontal disease associated with diabetes. *J Periodontol Res.* 1996;31(7):508-515.
20. Ryan ME, Ramamurthy NS, Golub LM. Tetracyclines inhibit protein glycation in experimental diabetes. *Adv Dent Res*. 1998;12(2):152-158.
21. Brownlee M. Glycation products and the pathogenesis of diabetic complications. *Diabetes Care*. 1992;15(12):1835-1843.
22. Dorfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. *J Clin Periodontol*. 2004;31(5):396-401.
23. Fiehn NE, Larsen T, Christiansen N, et al. Identification of periodontal pathogens in atherosclerotic vessels. *J Periodontol*. 2005;76(5):731-736.
24. Dögan B, Buduneli E, Emingil G, et al. Characteristics of periodontal microflora in acute myocardial infarction. *J Periodontol*. 2005;76(5):740-748.
25. Rose LF, Mealey BL, Genco RJ, et al (eds). *Periodontics: Medicine, Surgery, and Implants.* St Louis, Mo: CV Mosby; 2004:848.
26. Kozarov EV, Dom BR, Shelburne CE, et al. Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis*. *Arterioscler Thromb Vasc Biol*. 2005;25(3):E17-E18.
27. Deliargyris EN, Madianos PN, Kadoma W, et al. Periodontal disease in patients with acute myocardial infarction: prevalence and contribution to elevated C-reactive protein levels. *Am Heart J*. 2004;147(6):1005-1009.
28. Offenbacher S, Beck J. A perspective on the potential cardioprotective benefits of periodontal therapy. *Am Heart J.* 2005;149(6):950-954.
29. Genco RJ, Offenbacher S, Beck J, et al. Cardiovascular disease and oral infections. In: Rose LF, Mealey BL, Genco RJ, et al (eds). *Periodontal Medicine*. Hamilton, Ontario, Canada: BC Decker, Inc; 2000:71-74.
30. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105(9):1135-1143.
31. Kuramitsu HK, Kang IC, Qi M. Interactions of *Porphyromonas gingivalis* with host cells: implications for cardiovascular diseases. *J Periodontol.* 2003;74(1):85-89.
32. Miyakawa H, Honma K, Qi M, et al. Interaction of *Porphyromonas gingivalis* with low-density lipoproteins: implications for a role for periodontitis in atherosclerosis. *J Periodontol Res.* 2004;39(1);1-9.
33. Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol.* 2003;23(7):1245-1249.
34. Pussinen PJ, Alfthan G, Tuomilehto J, et al. High serum antibody levels to *Porphyromonas gingivalis* predict myocardial infarction. *Eur J Cardiovasc Prev Rehabil.* 2004;11(5):408-411.
35. Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. *Stroke*. 2004:35(9):2020.
36. Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. *Stroke*. 2004;35(2):496-501.
37. Desvarieux M, Demmer RT, Rundek T. Periodontal microbiota and carotid intima-media thickness; the oral infections and vascular disease epidemiology study (INVEST). *Circulation*. 2005;111(5):576-582.
38. Fuster V, Moreno PR, Fayad ZA, et al. Atherothrombosis and high risk plaque. Part I: Evolving Concepts. *J Am Coll Cardiol.* 2005;46(6):937-954.
39. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347(20):1557-1565.
40. American Heart Association. Inflammation, Heart Disease

and Stroke: The Role of C-Reactive Protein. Nov 2005. Available at: http://www.americanheart.org/presenter.jhtml?identifier=4648. Accessed Nov 18, 2005.
41. Shishehbor MH, Bhatt DL. Inflammation and atherosclerosis. *Curr Atheroscler Rep.* 2004;6(2):131-139.
42. Smith SC Jr, Anderson JL, Cannon RO, et al. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: report from the clinical practice discussion group. *Circulation.* 2004;110(25):E550-E553.
43. D'Aiuto FD, Parkar M, Andreou G. Periodontitis and systemic inflammation: Control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res.* 2004;83(2):156-160.
44. Iwamoto Y, Nishimura F, Soga Y, et al. Antimicrobial periodontal treatment decreases serum C-reactive protein, tumor necrosis factor-α, but not adiponectin a levels in patients with chronic periodontitis. *J Periodontol.* 2003;74(8):1231-1236.
45. Cobb CM, Callan DP. Flashpoint in periodontics: patient referral. *Triage*. 2005;1(2):12-16.
46. Brown DL, Desai KK, Vakili BA, et al. Clinical and biochemical results of the metalloproteinase inhibition with subantimicrobial doses of doxycycline to prevent acute coronary syndromes (MIDAS) pilot trial. *Arterioscler Thromb Vasc Biol.* 2004;24(4):733-738.
47. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for health-care professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003;107(3):499-511.

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THE SIGNIFICANCE OF PERIODONTAL INFECTION IN CARDIOLOGY

3 CEUs

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1. About half of patients presenting with myocardial infarction, MI, do not have "classic" risk factors for cardiovascular disease, CVD. One risk factor for MI that is not currently considered a "classic" or major risk factor for CVD is:

❑[a] Diabetes
❑[b] Periodontal disease
❑[c] Low HDL cholesterol
❑[d] Elevated LDL cholesterol

2. The intervention trials necessary to prove a cause-and-effect relationship between periodontal disease and CVD:

❑[a] Were completed in 1999
❑[b] Will be completed at the end of 2006
❑[c] Have not been contemplated at this time
❑[d] Are currently underway or about to be funded

3. The earliest change preceding the formation of atherosclerotic lesions is:

❑[a] Activation by macrophages
❑[b] Increased endothelial permeability
❑[c] Infiltration by lipid-filled macrophages
❑[d] Increasing numbers of smooth muscle cells

4. The marker of vascular inflammation that appears to be most closely associated with greater risk for myocardial infarction is:

❑[a] TNF-α
❑[b] hsCRP
❑[c] Cholesterol levels
❑[d] Matrix metalloproteinases

5. All the following statements are true EXCEPT:

❑[a] If hsCRP level is lower than 2.0 mg/L, a person has a low risk of developing cardiovascular disease within the next 10 years.
❑[b] If hsCRP is between 1.0 and 3.0 mg/L, a person has an average risk of developing cardiovascular disease within the next 10 years.
❑[c] If hsCRP is higher than 3.0 mg/L, a person is at high risk of developing cardiovascular disease within the next 10 years.
❑[d] If hsCRP level is lower than 1.0 mg/L, a person has a low risk of developing cardiovascular disease within the next 10 years.

continued on page 35

6. All the following are implicated in the theorized relationship between periodontal disease and a systemic response EXCEPT:

❑[a] A genetically programmed viral response
❑[b] Activation of proinflammatory mediators
❑[c] A hyperinflammatory response to periodontal pathogens
❑[d] Seeding of live periodontal bacteria from the oral cavity to vessel walls

7. Which of the following combinations of bacteria did University of Florida researchers recently demonstrate are capable of adapting to the vasculature and living within human atherosclerotic lesions?

❑[a] *Streptococcus intermedius* and *Actinobacillus actinomycetemcomitans*
❑[b] *Porphyromonas gingivalis* and *Actinobacillus* actinomycetemcomitans
❑[c] *Tannerella forsythia* and *Campylobacter rectus*
❑[d] *Prevotella intermedia* and *Treponema denticola*

8. One study found that individuals with severe periodontitis had a ____ times greater risk of ischemic stroke than subjects with mild periodontitis or healthy subjects.

❑[a] 1.3 ❑[b] 2.3
❑[c] 4.3 ❑[d] 4.5

9. All the following are thought to play roles in endothelial dysfunction that leads to atherosclerosis EXCEPT:

❑[a] Osteoporosis
❑[b] Genetic alterations
❑[c] Elevated plasma homocysteine concentrations
❑[d] Elevated and modified low density lipoprotein, LDL, cholesterol

10. If a person's cardiovascular risk score — judged by global risk assessment — is in the intermediate range (10% to 20% in 10 years), what test/measurement can help predict a cardiovascular and/or stroke event and help direct further evaluation and therapy?

❑[a] HbA1c ❑[b] HDL
❑[c] hsCRP ❑[d] Blood pressure

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Original Article

STRATEGIES FOR DENTAL HYGIENIST AND NURSE COLLABORATION IN TARGETING PERIODONTAL AND CARDIOVASCULAR DISEASES

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Abstract

This article presents the background and rationale for proposing a novel model for health care specifically targeting periodontal and cardiovascular disease (CVD) by using dental hygienists and nurses as point-of-care screeners. It is estimated that nearly 60% of total mortality in the United States is related to CVD[1], and it can be projected that at least 60 million adults (18 years or older) have periodontal disease of moderate to advanced severity.[2] Research reported during the last five years implicates the potential role of periodontal infection in increasing the risk for atherosclerosis which predisposes individuals to CVD. Although the relationships between the exposure of periodontal infection and cardiovascular outcomes are uncertain at this time, what has become apparent is that the periodontal bacteria/host interaction and its relationship to systemic conditions, such as smoking, diabetes, obesity, and hypertension, are highly complex.

However complicated and poorly understood these interrelationships may be, recent research suggests there is a clustering of variables (i.e., classic risk factors for CVD, different levels of periodontal pathogens, antibodies to those pathogens, and cardiovascular outcomes) that may represent the presence of specific syndromes and may more appropriately describe the link between periodontal disease and CVDs.[3] The perspective that periodontitis and CVD may be part of a clustering of interrelated variables is unique and intriguing. It also provides a clear direction for the kind of future research necessary to illuminate a more certain profile of individuals at risk for CVD, which deserves the attention of all medical and dental professionals in formulating new CVD management strategies.

This article proposes that nurses and dental hygienists are very well positioned to work in transdisciplinary collaboration to perform *bilateral point-of-care screening* to intercept patients at risk for periodontal and CVD. Examples of intervention opportunities are provided and readers are challenged to consider what may be possible if traditional professional boundaries are abandoned in favor of transdisciplinary care.

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(A complimentary copy of this article may be downloaded at www.thesystemiclink.com.)

Key words: Dental hygienist, nursing, screening, cardiovascular disease, dentistry, collaboration

With more than 2,600 Americans dying of CVD each day,[1] at a rate of one death every 34 seconds,[1] medical practitioners and policymakers are currently facing statistics on CVD that are daunting. This comes at a time when both public and private sectors are calling for health care promotion and primary prevention strategies that will preempt the incidence and severity of chronic diseases and conditions. Indeed, wellness instead of health repair has become the battle cry in public health arenas and at the center of consumer demands. However, instead of primary prevention to preempt the beginning of disease, the best option we currently have is secondary prevention aimed at minimizing the loss or disability resulting from chronic diseases. The widespread adoption of progressive disease management strategies that incorporate health wellness models and primary prevention still seems

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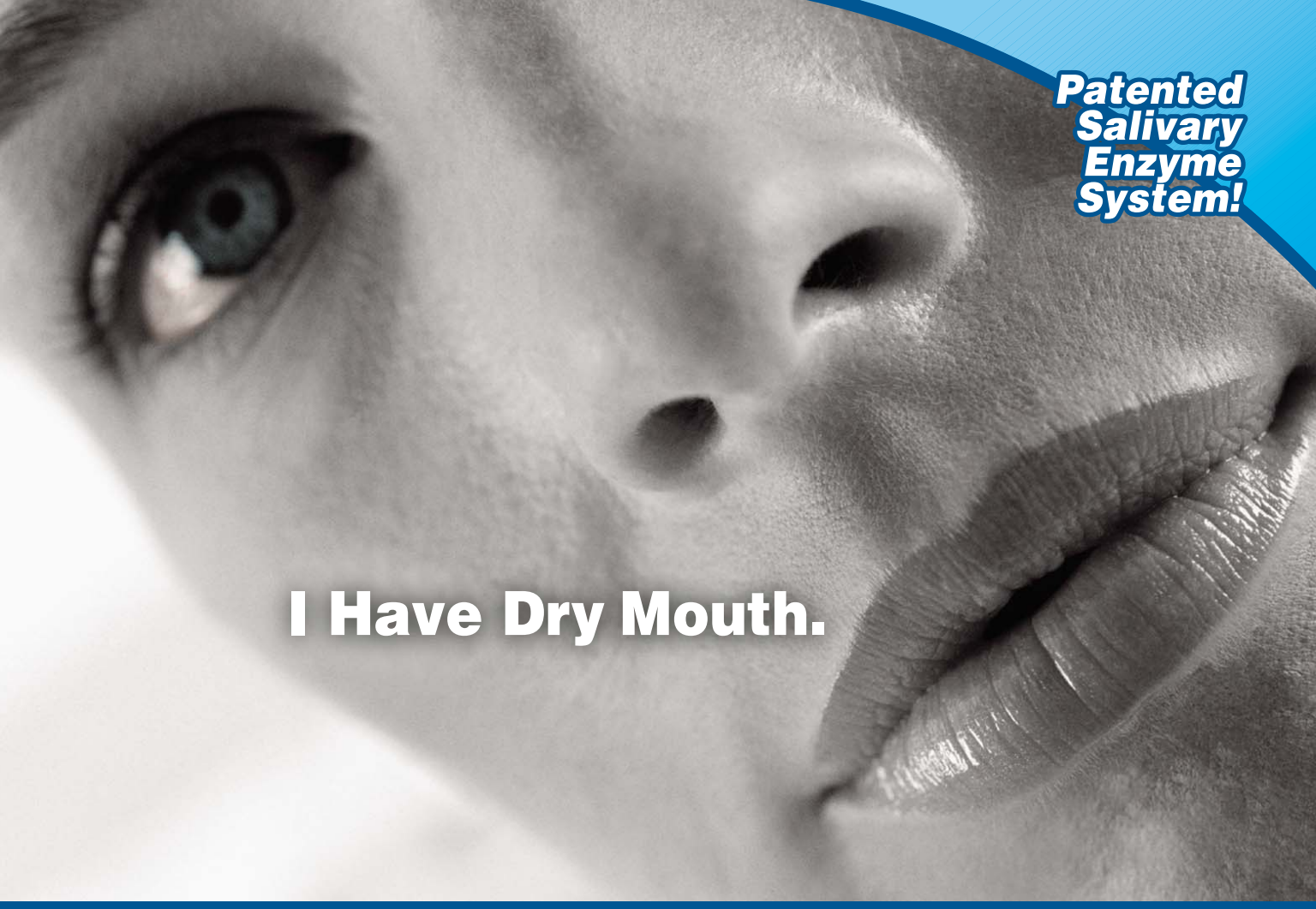

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far away.

Our capacity to provide even secondary preventive care is challenged beyond the capacity of our current health-care delivery system. Unfortunately, the outlook for the future may be even more dismal. As a group, the massive population of baby boomers are living longer, but living with multifactorial diseases like hypertension and diabetes which already tax the health-care system. In addition, the explosive increase in the prevalence of obesity and type 2 diabetes and their related complications, such as hypertension, hyperlipidemia, and atherosclerosis, and an alarming increase in unattended risk factors in younger populations will fuel the CVD epidemic for many years to come.[1] Given the projections of the incidence of CVD expected during the next 20 years,[1] the present way of delivering health care may soon be incapable of treating patients with already diagnosed CVD, and primary prevention aimed at intercepting patients at risk for CVD, our nation's number one killer, is a real long shot. The development of effective and efficient intervention strategies that address the multifactorial risk associated with chronic diseases and conditions like CVD is overdue. It is time to think beyond traditional models of care. At the heart of this health-care campaign may very well be one of the most powerful models of care ever mobilized — bilateral point-of-care screening, which relies on collaboration between dental hygienists and nurses in identifying and triaging patients at risk for systemic inflammation and chronic diseases, such as periodontitis and CVD.

CVD Statistics Going the Wrong Way

More than 70 million Americans have CVD,[1] which translates into one in four people with some form of CVD, including 7 million people with coronary heart disease (CHD) (myocardial infarction, angina pectoris), and more than 5 million people with stroke.[1] Table 1 chronicles a series of alarming statistics related to the prevalence, incidence, and mortality of CHD and stroke.[1] Even more frightening are the statistics related to the failure to assess CVD risk and to diagnose CVD. As an example, research indicates that for 50% of men and 64% of women who died suddenly of CHD, there was no previous recognition of the disease.[4] Furthermore, it was found that a significant proportion of the population with identified risk factors for CVD were not diagnosed with CVD and include individuals who are not being treated for CVD adequately.[4] Other studies have found that among insured people, 29% of adults with hypertension and 51% of adults with high cholesterol had undiagnosed CVD.[4] For the uninsured, projections of CVD prevalence were even more pronounced, with 41% of uninsured people having undiagnosed hypertension and 71% having undiagnosed hypercholesterolemia,[4] both highly recognized major risk factors for CVD.

There is a new twist to the etiology of CVD — about half of the patients presenting with myocardial infarctions (MI) do not have classic risk

Table 1
Alarming Statistics on the Prevalence, Incidence, and Mortality of Coronary Heart Disease and Stroke.[1]

Coronary Heart Disease:

- At current rates, an estimated 700,000 Americans will have a new coronary event, and 500,000 will have a recurrent event each year.
- The estimated number of years of life lost because of a heart attack is 11.5.
- 25% of men and 38% of women will die within 1 year after having an initial recognized MI.
- Individuals who survive the acute stage of a heart attack have a chance of illness and death that is 1.5 to 15 times higher than that of the general population.
- Within 6 years after a recognized heart attack:
  - 18% of men and 35% of women will have another heart attack.
  - 7% of men and 6% of women will experience sudden death.
  - 22% of men and 46% of women will be disabled with heart failure.
  - 8% of men and 11% of women will have a stroke.
- This year the estimated direct and indirect cost of CVD is $393.5 billion.

Stroke:

- On average, someone in the United States has a stroke every 45 seconds and every 3 minutes someone dies of a stroke.
- Stroke accounted for more than 1 of every 15 deaths in the United States in 2002.
- Each year, about 500,000 people experience their first stroke and 200,000 experience recurrent strokes.
- 14% of people who survive a first stroke or transient ischemic attack will have another within 1 year.
- 22% of men and 25% of women who have an initial stroke die within one year.
- 8% to 12% of ischemic strokes and 37% to 38% of hemorrhagic strokes result in death within 30 days.
- The estimated direct and indirect cost of stroke is $56.8 billion in year 2005.

factors for CVD.[5] And contrary to the long-held belief that CVD is primarily induced by hypercholesterolemia, high cholesterol is relevant in only 50% of patients with coronary artery disease (CAD).[6] As a result, researchers are aggressively pursuing other biological mechanisms that may implicate less obvious, more novel risk factors for CVD.

In Search of Novel Risk Factors for CVD

One of the biological mechanisms under investigation is the role periodontal infection may play in increasing the risk for CVD. During the last 20 years, many case-control and cross-sectional studies have shown have association between periodontal disease severity and CVD.[7] It has been known for some time that there is a biological gradient between periodontal infection and the incidence of CHD and a dose relationship between various levels of bone loss and the cumulative incidence of angina and MI.[8]

Although many research findings point to intriguing evidence of a relationship between periodontal disease and CVD, a cause-and-effect relationship has yet to be proven. Experts at the 2003 American Academy of Periodontology (AAP) Workshop on Contemporary Science in Clinical Periodontics concluded that although there was a moderate level of evidence to suggest that periodontal disease is associated with CVD, additional large-scale longitudinal epidemiological and intervention studies are necessary to validate the association.[9] What still remains a mystery is whether the association is causative or because of etiological factors common to both disease processes.[9] The consensus opinion of the 2003 workshop stated there was insufficient evidence to support advising patients that periodontal treatment could prevent the onset or progression of atherosclerosis-induced diseases like CVD and stroke.[9]

Since the consensus findings of the 2003 AAP workshop, mounting evidence reported in dental and medical journals seems to strengthen the supposition that periodontal bacterial pathogens and the resulting host immune response are directly implicated in the development of atherosclerosis and in the increased risk for cardio- and cerebrovascular events.[10-15] The Oral Infections and Vascular Disease Epidemiology Studies (INVEST) published within the last few years have provided more substantial evidence that periodontal disease may actually accelerate the development of atherosclerosis-related diseases (i.e. CVD and stroke).[16] The INVEST studies also reported that patients with significant periodontal bacterial burden had increased carotid intima-media thickness (IMT),[16] which is an indicator of subclinical (undetected) atherosclerosis and a precursor to CVD.

One of the most reliable markers of systemic inflammation is high sensitivity C-reactive protein (hsCRP), which is one of the acute phase proteins that is produced by the liver in response to ischemia, trauma, burns, infections, and other inflammatory conditions.[7] C-reactive protein (CRP) is an independent risk factor for CVD.[17] The growing consensus is that testing CRP levels in the blood with high sensitivity assay (hsCRP), which is now widely available, can consistently predict new coronary events in patients with unstable angina and acute MI.[18] It has also been suggested that increased hsCRP will elevate an individual at intermediate risk for CVD within 10 years to a higher risk category.[18] Recent research indicates that there may be a gradient effect between the extent and severity of periodontal disease and elevated levels of hsCRP[19] and that the presence of CVD seems to be highest in those individuals in whom periodontal disease co-exists with elevated hsCRP.[20] Patients with periodontitis have increased systemic levels of hsCRP and fibrinogen, both of which affect coagulation, platelet activation, and aggregation contributing to atheroma formation, thereby increasing the risk for CVD.[21,22]

It is true that randomized controlled clinical trials to demonstrate the potential cardiovascular benefits of periodontal treatment are needed before sweeping changes in health-care policy can be established. Some of this research, in fact, may be on the way. The National Institute of Dental and Craniofacial Research (NIDCR) has just completed but not yet reported the findings of a study of 400 participants called PACE (Periodontitis and Cardiovascular Events) to determine if treating periodontal infections will lead to fewer MIs, cardiac revascularization, fatal coronary disease, unstable angina and hospitalized ischemic stroke.[23] This pilot clinical trial, involving investigations at five university treatment facilities, will provide supporting data for the development of a larger randomized clinical trial that will include about 4,000 participants from 15 academic centers across the United States.[23]

Another study that is especially intriguing is being conducted at Boston University. Also sponsored by NIDCR, this study is designed to determine whether effective treatment of periodontal disease improves endothelial

function and reduces inflammation.[24] The term being used to describe this kind of approach to therapy is *reversible atherosclerosis* (S. Amar, oral communication, Nov 2005). The investigators are halfway into clinical trials, with results expected in 2009.

The overwhelming statistics related to the prevalence, incidence, and mortality of CVD, in combination with the emerging body of evidence implicating periodontal infection as a potential risk correlate for CVD, provides an unprecedented opportunity for dental and medical collaboration. This includes prevention, early identification and progressive treatment of CVD, and recognition of novel risk factors related to systemic inflammation arising from chronic infections like periodontitis. Dental hygienists and nurses have a major role to play in bringing about this level of action. Although well-supported recommendations for preventing heart disease and stroke have been available for more than 50 years, these guidelines have not been well implemented by physicians and patient compliance is poor.[25] For example, the American Heart Association (AHA) recommends that adults 40 years of age or older with no history of CVD be assessed for their risk for CHD every five years.[4] Unfortunately, research among primary care physicians found that such an assessment has not been widely implemented.[4] Mobilizing point-of-care providers such as dental hygienists and nurses to perform risk assessment for periodontal disease and CVD may net the greatest gains in progressive prevention and detection of these diseases.

Perhaps one of the most compelling statistics to support ramping up dental hygienist and nurse collaboration in integrating risk assessment protocols is that 250,000 sudden deaths from CHD occur each year without hospitalization or in the absence of any previous history of CHD.[26] For these victims, there was no opportunity for treatment because no one identified their risk for CVD. In effect, death became the first sign of CVD. Collectively, the CVD statistics and emerging evidence of a relationship between periodontal disease and CVD provides a strong justification for using dental hygienists and nurses to provide progressive point-of-care intervention strategies.

Robust Reduction of Risk for CVD

It has been said that, "No matter what advances there are in high-technology medicine, the fundamental message is that any major reduction in deaths and disability from CVD will come from prevention and not cure. This must involve robust reduction of risk factors."[27] Because atherosclerosis is associated with the majority of cases of CVD, robust reduction of risk factors for CVD necessarily begins with reducing the risk for atherosclerosis.

The development of an atherosclerotic lesion, which is implicated in the majority of CVD cases,[9] is thought to be a multifactorial and complex process.[6] Atherosclerosis is an inflammatory sequela, arising from injury, leading to dysfunction of the endothelial cells lining the lumen of an artery.[6] The degree of endothelial dysfunction depends on the cumulative burden and severity of cardiovascular risk factors, including the cumulative burden of infections[6] like periodontitis. Several causes of endothelial dysfunction that lead to atherosclerosis and, therefore, increased risk for CVD include, but are not limited to, elevated low-density lipoprotein, cigarette smoking, diabetes mellitus, and hypertension.[6] Beck and Offenbacher recently wrote that, "The problem regarding CVD management is that since it requires decades to initiate and propagate, it also requires sustained intervention to prevent or treat."[3] So true, yet without developing and sustaining primary prevention and health promotion intervention strategies that address all risk factors including those implicated in systemic inflammation, we will continue to see increasing numbers of people with CVD risk factors, increasing numbers of first and recurrent heart attack and stroke victims, and increasing numbers of people who die from CVD.[28]

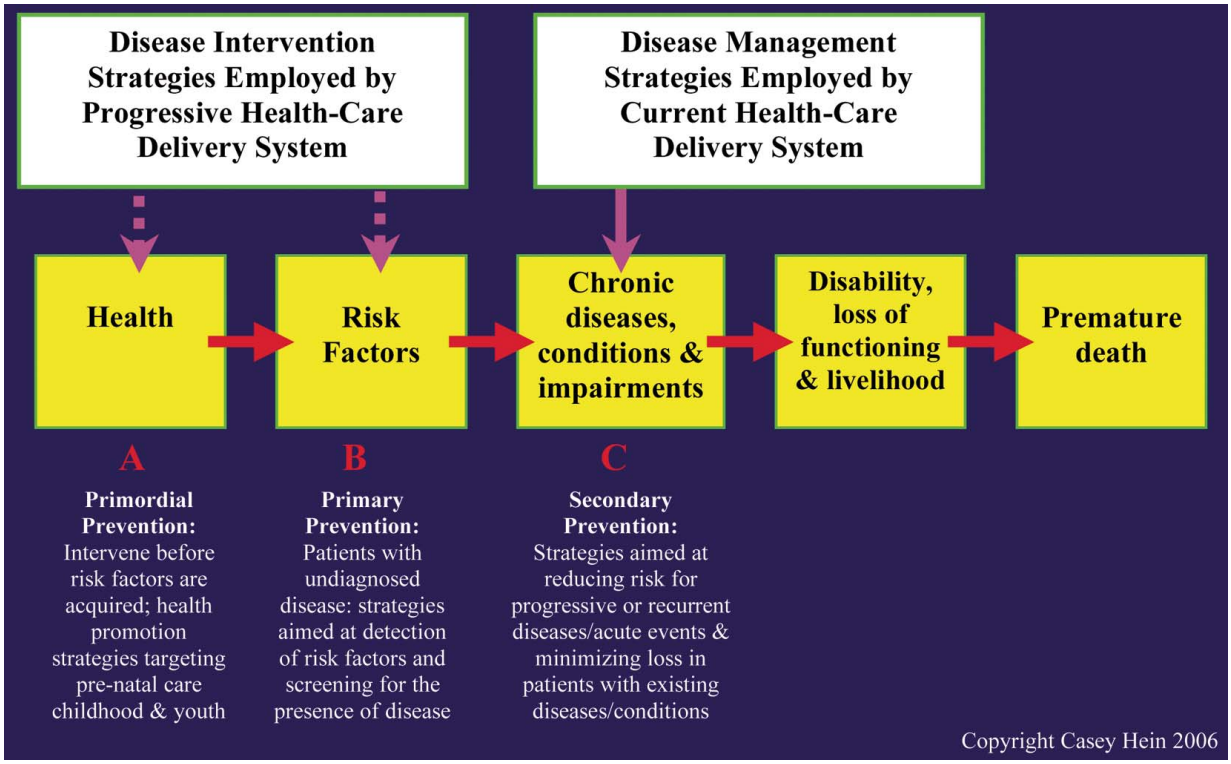
When *Healthy People 2010* was published in 2000, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) shared joint responsibility for moving the nation toward achieving the goals set forth in the report and periodically reporting the progress over the course of the decade.[28] The *Healthy People 2010 Heart and Stroke Partnership* set into place four goals based on different intervention approaches for prevention, detection, and treatment of risk factors related to CVD:[25]

- Prevention of risk factors
- Detection and treatment of risk factors
- Early identification and treatment of heart attacks and strokes
- Prevention of recurrent cardiovascular disease

Recommendations in the form of clinical practice guidelines for detecting and treating risk factors and preventing heart disease and stroke have been published

Figure 1

Points of intervention opportunities in targeting periodontal and cardiovascular disease



by the AHA/American Stroke Association (ASA), the American College of Cardiology (ACC), and the National Heart, Lung, and Blood Institute (NHLBI).[25] These recommendations embody three points of intervention of CVD (see Figure 1):

- Primordial prevention of CVD, Point A, includes the promotion of a combination of favorable health habits and conditions that protect against the development of CVD.[25] Cardiovascular health promotion targets individuals at any age who have not yet developed risk factors because the intervention occurred before the risk factors began to incite changes in the vasculature that lead to CVD.[25] Such interventions should start in childhood — some would argue even during gestation — and continue throughout adulthood to prevent risk factors from ever developing.[25]
- Primary prevention, Point B, is intended to prevent a first heart attack or stroke by detecting and treating risk factors of individuals with CVD risk factors but no clinical manifestations of CVD.[25]
- Secondary prevention, Point C, aims to reduce the risk for recurrent heart attacks or strokes by treating CVD and the risk factors of individuals with established CVD, including survivors of CVD events.[25]

The probability of achieving the risk prevention, reduction, and treatment goals contained in Healthy People 2010 and implementing the clinical practice guidelines set forth by the AHA/ASA, the ACC, and the NHLBI may be significantly increased with a collaborative model of care that aligns dental hygienists and nurses in the integration of clinical protocols and bilateral screening for CVD and periodontitis.

Mobilizing Dental Hygienists in Collaboration with Nurses

In fiscal year 2005, Congress appropriated $45 million for the Heart Disease and Stroke Prevention Program.[29] The CDC, which has advocated for the adoption of a long-term national health-care policy that includes primary prevention of premature atherosclerosis,[29] currently funds risk reduction programs in 32 states and the District of Columbia.[29] The priorities of these programs include control of high blood pressure and high cholesterol.[29] What seems to be missing in these funding priorities are

strategies for reducing systemic inflammation, which is becoming increasingly recognized as a serious threat to cardiovascular wellness. Although the CDC acknowledges that collaboration in bringing about cardiovascular health is key, there is no reference to dental-medical collaboration or dental hygienist-nurse collaboration. This may represent a departure from the Surgeon General's recommendations for interdisciplinary care among dental and nondental care providers embodied in the *Oral Health in America* report published in 2000.[30] Bypassing this collaborative model of care may forfeit the potential of a valuable alliance in providing primary prevention in daily patient care.

Health-care usage patterns indicate that individuals tend to seek routine and preventive oral health care on a more frequent and regular basis than routine and preventive medical care.[4] Glick and Greenberg[4] recently reported a national probability sample that estimated that among people aged 40 to 85, about 25% reported having no history of CHD, heart attack, stroke, or angina, and no previous diagnosis of hypertension or high cholesterol levels. A number of these people with unidentified risk factors had not seen a physician within the previous 12-month period; however, they had seen a dentist within that same time period.[4] When the researchers applied the Framingham-based risk calculation to this sample group, 18.3% of men were found to be at increased risk for a first CVD event.[4] The findings from this study substantiate that dental-care providers are uniquely positioned to intercept CVD in patients who are unaware of their increased risk. Unfortunately for many people with undiagnosed CVD, it is hospitalization for an acute coronary event that provides the "teachable moment" for secondary prevention of a recurrence. The dental practice setting could provide the "teachable moment" for interception of those individuals with unidentified risk factors for CVD, a primary prevention strategy that is easily integrated into daily patient care.

Assessing the Risk of Periodontal Disease as an Exposure for Systemic Injury

Unfortunately, many practitioners still hold the view that periodontal disease is the clinical outcome of interest rather than a potential contributor to a greater disease process within the human body. This philosophy of practice may prevent clinicians from taking responsibility and becoming accountable for periodontal-systemic outcomes.

If the strength of evidence from epidemiological studies and intervention trials net the results that many researchers have speculated, it seems inevitable that the classification of inflammatory periodontal disease will have to be modified to reflect the level of risk it may pose for a potential exposure event for atherosclerosis-related systemic diseases such as CVD. Along those lines, various researchers have already developed concepts that attempt to quantify the risk of systemic consequences of periodontal infection. One of the most notable is the Periodontal Index for Risk of Infectiousness (PIRI).[31,32]

The PIRI computes the amount of ulcerated subgingival space exposed to the infection burden and the potential systemic threat that the bacterial challenge poses to patients with periodontal disease.[32] Using the PIRI to determine a patient's level of risk for periodontal-systemic consequences, individual patients are assigned penalty points. By taking into account the probing depths of the deepest periodontal lesions and their number per patient, this methodology gives a quick, gross estimation of the surface area of the interface between the subgingival biofilm and the epithelial walls of the periodontal niches.[32] This provides a relative value for the level of individuals' risk for the release of proinflammatory mediators from the periodontium.[31,32] When researchers used the PIRI to quantify the level of risk that periodontal infection posed to cardiovascular health, they found a significant dose response relationship between increasing PIRI scores and the presence of CAD; specifically that subjects who had the highest PIRI scores had a 13.8 times greater risk of having CAD than patients with the lowest scores.[32]

The theory that periodontal infections predispose certain individuals to accelerated progression of carotid atherosclerosis (and therefore increased risk for stroke), MI and CVD may no longer be a stretch. To that end, it seems entirely appropriate for nondental practitioners to begin to categorize infection from periodontal origin as a risk correlate for CVD. It also seems right that nondental care providers start to recognize novel risk factors like elevated hsCRP, which is implicated in both CVD and periodontitis. Elevated levels of hsCRP have been shown to predict future coronary events and may add predictive value to testing for cholesterol levels.[33] In the future, medical and dental practices may screen patients to quantify certain markers of systemic inflammation implicated in diseases like CVD and periodontitis. Analyzers designed to monitor hsCRP and HbA1c are now available to use in-office or chairside, which can provide the mechanism for onsite

Promote Health

Oral health may be influenced by plaque control, nutrition, fluoride exposure, hormonal changes, medical conditions, medications and/or medical treatments. Oral bacteria (plaque) produce acids that may destroy tooth enamel after long periods of time. Frequency of a highly acidic oral environment increases the risk for dental disease. In many cases, dental disease can be prevented.

Prevention starts as early as primary tooth development. Oral health care should be promoted throughout pregnancy, infancy, childhood, teen and adult life. Special attention to oral care should be enforced when certain medical conditions may influence the oral environment. Increased awareness of potentially unhealthy oral conditions may help prevent oral infection, or promote early detection, thereby motivating improvement and management.

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screening for markers of systemic injury of patients in dental and medical practices. These technologies place into the hands of medical and dental practitioners tools for both primary and secondary prevention of cardiovascular events, which are easily incorporated into patient care.

Should future events dictate that periodontal treatment is medically necessary to decrease the risk for systemic complications, such as CVD and ischemic stroke, it seems likely that the demand for periodontal services will increase. This, in turn, will prompt significant changes in insurance and reimbursement mechanisms. Assessing risk properly and triaging patients to appropriate health-care providers is pivotal in bringing about elimination and reduction of patients' risk for both periodontal and cardiovascular diseases and will require highly integrated dental-medical care. The actual implementation of periodontal medicine most appropriately falls to dental hygienists and nurses who are uniquely well positioned to play a key protective role by preventing the initiation, escalation, and/or acceleration of systemic events via bilateral point-of-care screening.

Building the Case for Dental Hygienist and Nurse Bilateral Point-of-Care Screening

Screening for individuals at risk for CVD and integrating the research findings associated with the theorized link between periodontal disease and CVD exceeds the capacity of any one profession. Indeed, it will take practitioners from both the medical and dental side, at all levels, to implement scientifically justified prevention strategies. It will also require targeted interventions that are multidisciplined for a sustained period of time to change the risk profile of an individual who has identified risk factors for CVD and more extensive and sustained interventions for those who have already suffered a coronary event. Accordingly, there needs to be a purposeful shift from prevention and treatment of two distinct diseases (i.e., dental practitioners' sole focus on periodontal disease and medical practitioners' exclusive focus on CVD) to a transdisciplinary model of care. These overlapping boundaries of care are centered around prevention and treatment of a cluster of interrelated clinical signs and symptoms of chronic inflammation, with CVD, ischemic stroke, and periodontal disease being part of this cluster. Hypertension and diabetes (or insulin resistance), when present, may also be part of this cluster of interrelated signs and symptoms of chronic inflammation. New research may actually add validity to the assertion that health-care providers may need to start thinking of CVD and periodontal disease as part of a cluster of interrelated variables.[3]

Beck and Offenbacher[3] recently published a study that was designed to determine which CVD outcomes are affected by oral diseases and under what related circumstances individuals may be at greater risk for CVD.[3] Using a statistical technique called principal component analysis, the researchers explored the relationship and the strength of correlation between traditional risk factors for CVD (i.e., smoking, hypertension, obesity, and age), periodontal pathogen exposure levels (low to high), antibody levels to those pathogens (low to high) and cardiovascular outcomes. The authors noted four distinct biofilm microorganism-host response patterns and speculated that there is a clustering of variables (i.e., traditional risk factors for CVD, levels of periodontal pathogens and antibody levels) within those biofilm patterns that correspond to CVD outcomes.[3] In evaluating an individual's CVD health in comparison with the level of periodontal microorganisms and their antibody levels, the researchers found that IMT is more closely associated with antibody levels, and that stroke and CHD are more influenced by the level of periodontal microorganisms, especially when antibody levels are high.[3] Of particular interest was the finding that individuals with early periodontitis, low levels of periodontal microorganisms and high antibodies are more likely to have CHD and stroke than individuals with severe periodontitis, high levels of organisms, and high antibodies.[3] Elevated antibodies appeared to be associated with periodontal disease and chronic systemic conditions (i.e., CHD and diabetes). In conclusion, the researchers noted the importance of understanding the underlying relationships between oral infection and CVD and the implication of this in enabling better diagnosis, treatment, and management of CVD.[3] This research presents a unique perspective and an intriguing concept that should be considered by both medical and dental professionals in moving toward transdisciplinary prevention and management of CVD. The clustering of interrelated variables also represents a domain of periodontal medicine that must be shared and equally understood by point-of-care providers like nurses and dental hygienists. Both medical and dental professionals are responsible for implementing this information into clinical practice.

Ideas for Implementing Bilateral Point-of-Care Screening by Dental Hygienists and Nurses

Recognizing the points at which clinicians have an

opportunity to alter the course of disease is the key to the implementation of successful intervention strategies. Figure 1 illustrates various points of intervention and valuable therapeutic opportunities for dental hygienists and nurses.

Intervention Point A represents *primordial preventive* measures, including health promotion (therapeutic seeding) directed toward lifestyle changes that emphasize exercise, weight loss or control, and knowledge of risk factors in healthy patients. Examples of therapeutic seeding include novel patient education strategies aimed at preventing obesity, smoking, sedentary behavior, and chemical addictions. In addition, education of certain ethnic populations known to be at greater risk for chronic diseases and patients with suspected genetic predisposition to periodontal disease is vital. Primordial prevention also includes proactive educational campaigns targeting such things as healthy nutrition and physical activity. Calibration of these messages between the nursing and dental hygiene professions would reinforce the same important patient information.

Intervention Point B corresponds to *primary prevention* and includes screening for the presence of an undiagnosed disease like diabetes and risk for CVD and ischemic stroke. Screening tools such as the Framingham global risk assessment, in-office hsCRP and HbA1c testing, the use of body mass index (BMI) tracking, and diabetic profiling, fall into this prevention category. This level of care has the potential to significantly impact chronic disease trends, but only if integrated screening can be incorporated into dental and medical practices. This transdisciplinary model of care adds significant value to the positions of both dental hygienists and nurses as preventive specialists.

Intervention Point C is *secondary prevention* and includes the treatment of chronic conditions in an attempt to minimize disability and/or the loss of function in individuals with already diagnosed diseases. Among other things, secondary prevention includes treatment of periodontal disease, metabolic control of diabetes, and management of hyperlipidemia and hypercholesterolemia with the goal of reducing disability or increasing compromised function.

With consumer demand for wellness and newly emerging philosophies of care that embrace the wellness model over the repair model, we can expect to see a push toward developing primary and secondary prevention strategies that pre-empt the incidence and severity of chronic disease. The implementation of bilateral point-of-care screening by dental hygienists and nurses provides a potential clinical pathway that may have a profound effect on disease prevention or, possibly, disease reversal. Ideas relative to implementation of bilateral point of care screening by dental hygienists and nurses are as follows:

- *It has been observed that the risk for CVD is highest in individuals with periodontitis, elevated hsCRP concentrations, and serum antibody levels to periodontal pathogens.[20] This observation suggests that periodontitis increases CVD risk, primarily in those individuals who react to periodontal infections with a profound systemic inflammatory and immune response.[20] Interestingly, it has also been suggested that patients exhibiting both periodontitis and elevated hsCRP levels are not necessarily those with the most severe periodontal disease.[20] Regardless, researchers have reported that treating periodontitis in patients with elevated hsCRP results in decreased levels and may, therefore, translate into decreased risk for CHD.[34]*

This information, in addition to other evidence concerning the relationship between hsCRP and periodontal disease, provides a compelling rationale for hsCRP testing by dental hygienists. These rationales include:

1. The use of hsCRP testing in dental offices may detect those individuals who present with less severe periodontal disease but react to periodontal infection with more profound systemic inflammation and immune response.
2. The use of hsCRP testing in dental offices may increase the detection of individuals at high risk for CVD and ischemic stroke beyond that of lipid testing (cholesterol) alone.[33]
3. The use of hsCRP testing in dental offices may allow improved identification of individuals who would benefit from statin therapy (cholesterol-lowering drugs).[33]
4. The use of hsCRP testing in dental offices may increase the rate of identification of those cardiac patients who are at greater risk for an acute coronary syndrome.[33]

- *Extensive periodontal disease and BMI were found to be commonly associated with increased hsCRP levels in otherwise healthy middle-aged adults, suggesting the need for both medical and dental diagnoses when looking for the sources of acute phase response in*

some patients.[35]

Nurses screening otherwise healthy middle-aged adults for elevated hsCRP and obesity as determined by BMI may identify those patients at high risk for periodontal disease. Conversely, dental hygienists screening for those periodontal patients who are obese may identify patients at risk for increased hsCRP levels. Both of these strategies represent secondary prevention.

- *Obesity is associated with multiple-risk factor syndromes, such as hypertension, hyperlipidemia, type 2 diabetes, periodontal disease, and atherosclerosis.*[36] *Among adults aged 18 and older, the prevalence of two or more risk factors increased from 23.6% in 1991 to 27.9% in 1999.*[1] *It is important to note that multiple risk factor syndromes increased for both men and women and across all race, ethnic, age, and education groups.*[1] *Among those with two risk factors in 1999, the most common combination was hypertension and high cholesterol (23.9%).*[1] *Among those with three risk factors, the most common combination was hypertension, high cholesterol, and obesity (32.5%).*[1]

Recognition by both nurses and dental hygienists of the interrelationships of the multiple-risk factor syndromes stated above allows for significantly greater bilateral interception of at-risk individuals, and the opportunity to triage, in both directions, those cases that require more aggressive care. Less than 12% of people say that a health-care provider has talked to them about the need for weight loss over the past year.[37] To that end, those practitioners who are reluctant to start dialogues with patients about weight control need to overcome their discomfort and begin to educate patients about the risks imposed by obesity.

- *Researchers found that, on average, adults who have experienced a coronary event had been small at birth and thin at 2 years of age, but then rapidly gained weight thereafter — a pattern of growth associated with insulin resistance in later life.*[38] *The researchers concluded the risk for coronary events is more strongly associated with the rate of childhood gain of BMI than to BMI attained in adulthood.*[38]

Dental hygienists and nurses who incorporate aggressive therapeutic seeding related to prevention of childhood obesity into pedodontics and pediatrics may have the most significant influence on risk for future adult coronary events. Nurses also need to recognize that the incidence of periodontal disease starting in youth is projected to increase parallel to childhood obesity trends.[39] The current epidemiologic trend indicates that this younger population subset may also become predisposed to chronic inflammatory diseases at a much younger age than their older cohorts,[39] which is significant for dental hygienists to consider when designing health promotion programs, including screening protocols.

- *With increasing severity of periodontitis, there is a progressive increase in left ventricular mass (a known independent predictor of CVD) in patients with essential hypertension. Researchers concluded that periodontal evaluation might contribute to refining cardiovascular risk assessment in patients with high blood pressure.*[40]

A valuable addition to the assessment of individual patients would be a nurse's recognition that hypertensive patients with increases in left ventricular mass might also be at increased risk for periodontal disease. Triage of such at-risk patients to dental care providers constitutes an excellent opportunity for collaboration with the dental profession. On the other hand, a dental practitioner's measurement of blood pressure can identify the presence of hypertension and/or level of the patient's hypertension control,[41] both of which represent cases that should be triaged to a medical practitioner.

- *Patients with diabetes are 2 to 5 times more likely, smokers are 3 to 7 times more likely, patients who report that parents or siblings lost their teeth at a young age may be 3 to 5 times more likely, and those with suspected genetic predisposition and who also smoke are 8 to 10 times more likely to develop periodontal disease.*[42]

These are the very individuals who are at significantly higher risk for periodontal disease and when seen by medical practitioners should be triaged to dental practitioners. It is fairly simple to include known risk factors (i.e., smoking, diabetes, and genetic predisposition) for periodontal disease that do not require intraoral examination as part of nurses' assessment of their patients.

- *Some investigators have found gingival inflammation may be considered a more significant risk factor for CVD than clinical attachment loss.*[43]

If nurses used a screening tool as simple as a wooden toothpick to check for gingival inflammation and bleeding of gingival margins or interproximal papillae, it seems reasonable that cases of gingivitis could be identified in medical settings. Treatment intervention at this point may decrease patients' risk for CVD and ischemic stroke. Conversely, it should be noted that dental hygienists' recognition that periodontal disease and gingivitis may increase a patient's risk for CVD or ischemic stroke is important if patient wellness is the outcome of interest.

- *Porphyromonas gingivalis has been implicated in several steps in the development of the atherosclerotic lesion.[44,45] In addition, hsCRP levels are highest in patients who are infected with periodontal pathogens.[46]*

Another opportunity, albeit rather unconventional, for intervention would be the incorporation of DNA probe and sensitivity testing to screen for *P. gingivalis* and other periodontal pathogens in medical practices. Taking a sample of subgingival plaque is performed by placing a paper point subgingivally and although this is an intraoral procedure, taking the sample is relatively noninvasive and may be easily taught to nondental care providers.

- *Recent research has found that radiographic evidence of severe periodontal bone loss was independently associated with nearly a four-fold increase in risk for the presence of carotid artery plaque.[47]*

This has considerable significance for the dental community. Patients with radiographical evidence of periodontal bone loss may be excellent candidates for referral to the medical side; the addition of hsCRP testing might add further validity to the need for referral. Conversely, patients with diagnosed atherosclerosis represent those who medical care providers should triage for periodontal evaluation and treatment.

Conclusion

Central to all these point-of-care intervention strategies is the assumption that dental hygienists and nurses have a keen awareness of the systemic affects of cumulative infection and the systemic inflammatory burden implicated in atherosclerosis formation. Bilateral point-of-care screening for periodontal disease and cardiovascular risk also supposes that health-care providers on both sides understand the contribution of periodontal infection to systemic inflammation and that prevention or treatment of periodontal disease will reduce the cumulative pathogen and inflammatory burden. As a result, these types of intervention strategies may decrease the morbidity associated with chronic diseases. These strategies also assume that dental hygienists and nurses are intensely aware of how chronic disease states jeopardize patients' oral health status.

No doubt screening and diagnostic technologies will some day soon make targeting those at risk a much more concrete science.Currently in development is a self-contained saliva test that would allow detection of periodontal and cardiovascular disease in dental offices, estimated to take no longer than 15 minutes to perform.[48] Until these types of non-invasive, efficient, and affordable tests of biological markers of chronic disease states are developed and commercialized, we must rely on traditional risk assessment of periodontal disease and CVD.

There is a significant body of evidence to support the concept of a cluster of interrelated signs and symptoms of chronic inflammation that includes periodontal disease and atherosclerosis-related diseases. To address this cluster of maladies, nurses and dental hygienists are uniquely positioned to deploy progressive disease intervention strategies within a collaborative framework that includes wellness promotion and primary prevention. Neither of these points of intervention are currently practiced in mainstream health care. Moving to a transdisciplinary model of care will no doubt be challenging. Proactive initiatives of the nursing and dental hygiene professions to achieve this goal should be a major focus of contemporary dental hygiene and nursing practice. Until there is reform of dental hygiene and nursing education that includes a strong oral-systemic component in the curriculum, the forerunners of this transdisciplinary model of care will most likely be individual dental hygienists and nurses who independently forge alliances to foster collaboration. These alliances will be comprised of practitioners who are committed to pursuing a wellness model of care, who are willing to abandon traditional professional boundaries, and who are willing to risk doing something yet uncharted to provide extraordinary patient care. For millions of people who are destined to lose their lives on their first encounter with CVD, mobilizing dental hygienists in collaboration with nurses to perform bilateral point-of-care screenings may significantly reduce premature death.

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References

1. American Heart Association. Heart Disease and Stroke Statistics-2005 Update. 2005. Available at: http://www.americanheart.org/presenter.jhtml?identifier=1928. Accessed Dec 6, 2005.
2. Cobb CM. Diagnosis and treatment of periodontal disease: a crisis of direction. *Triage*. 2005;1(1):15-20.
3. Beck JD, Offenbacher S. Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. *J Periodontol.* 2005;76(11 Suppl):2089-2100.
4. Glick M, Greenberg BL. The potential role of dentists in identifying patients' risk of experiencing coronary heart disease events. *J Am Dent Assoc.* 2005;136(11):1541-1546.
5. Koenig W. C-reactive protein: risk assessment in the primary prevention of atherosclerotic disease. Has the time come for including it in the risk profile? *Ital Heart J.* 2001;2(3):157-163.
6. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med.* 1999;340(2):115-126.
7. Rose LF, Mealey BL, Genco RJ, et al. (eds). *Periodontics: Medicine, Surgery, and Implants.* St Louis, Mo: CV Mosby; 2004:848-857.
8. Beck J, Garcia R, Heiss G, et al. Periodontal disease and cardiovascular disease. *J Periodontol.* 1996;67(10 Suppl):1123-1137.
9. Scannapieco FA, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. *Ann Periodontol.* 2003;8(1):38-53.
10. Dögan B, Buduneli E, Emingil G, et al. Characteristics of periodontal microflora in acute myocardial infarction. *J Periodontol.* 2005;76(5):740-748.
11. Fiehn NE, Larsen T, Christiansen N, et al. Identification of periodontal pathogens in atherosclerotic vessels. *J Periodontol.* 2005;76(5):731-736.
12. Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol.* 2003;23(7):1245-1249.
13. Dorfer CE, Becher H, Ziegler CM, et al. The association of gingivitis and periodontitis with ischemic stroke. *J Clin Periodontol.* 2004;31(5):396-401.
14. Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. *Stroke.* 2004;35(2):496-501.
15. Lalla E, Lamster IB, Hofmann MA, et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. *Arterioscler Thromb Vasc Biol.* 2003;23(8):1405-1411.
16. Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Stroke.* 2003;34(9):2120-2125.
17. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* 2005;352(16):1685-1695.
18. Smith SC Jr, Anderson JL, Cannon RO, et al. CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: Report from the Clinical Practice Discussion Group. *Circulation.* 2004;110(25):E550-E553.
19. Loos BG. Systemic markers of inflammation in periodontitis. *J Periodontol.* 2005;76(11 Suppl):2106-2115.
20. Mattila KJ, Pussinen PJ, Paju S. Dental infections and cardiovascular diseases: A review. *J Periodontol.* 2005;76(11 Suppl):2085-2088.
21. Wu T, Trevisan M, Genco RJ, et al. Examination of the relation between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, c-reactive protein, and plasma fibrinogen. *Am J Epidemiol.* 2000;151(3):273-82.
22. Slade GD, Offenbacher S, Beck JD, et al. Acute-phase inflammatory response to periodontal disease in the US population. *J Dent Res.* 2000;79(1):49-57.
23. US Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research. Periodontitis and Cardiovascular Events or "PAVE". Dec 2005. Available at: http://www.clinicaltrials.gov/ct/show/NCT00066053?order=2. Accessed Dec 11, 2005.
24. US Department of Health and Human Services, National Institutes of Health, National Institute of Dental and Craniofacial Research; Boston University. Impact of Gum Infection on Heart Disease. Dec 2005. Available at: http://www.clinicaltrials.gov/ct/show/NCT00093236?order=1. Accessed Dec 11, 2005.
25. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health. Cardiovascular Health: A Public Health Action Plan to Prevent Heart Disease and Stroke. Section 1. Heart Disease and Stroke Prevention: Time for Action. Evolution of Prevention Policy. June 2005. Available at: http://www.cdc.gov/cvh/Action_Plan/full_sec1_evolution.htm. Accessed Dec 11, 2005.
26. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health. Cardiovascular Health: A Public Health Action Plan to Prevent Heart Disease and Stroke. Section 1. Heart Disease and Stroke Prevention: Time for Action. Myths and Misconceptions. June 2005. Available at: http://www.cdc.gov/cvh/Action_Plan/full_sec1_myths.htm. Accessed Dec 11, 2005.
27. World Health Organization. The Atlas of Heart Disease and Stroke. 2005. Available at: http://www.who.int/cardiovascular_diseases/resources/atlas/en/. Accessed Dec 11, 2005.
28. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health. Cardiovascular Health: A Public Health Action Plan to Prevent Heart Disease and Stroke. Section 1. Heart Disease and Stroke Prevention: Time for Action; Healthy People 2010 Goals and Objectives. June 2005. Available at: http://www.cdc.gov/cvh/Action_Plan/full_sec1_hp2010.htm. Accessed Dec 11, 2005.
29. US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion. Preventing Heart Disease and Stroke, Addressing the Nation's Leading Killers 2005. Available at: http://www.cdc.gov/cvh. Accessed Dec 6, 2005.
30. Satcher D. US Department of Health and Human Services. Oral Health in America: A Report of the Surgeon General. May 2000. Available at: http://www.surgeongeneral.gov/library/oralhealth/. Accessed Nov 18, 2005.
31. Geerts SO, Nys M, De MP, et al. Systemic release of endotoxins induced by gentle mastication: association with periodontitis severity. *J Periodontol.* 2002;73(1):73-78.

32. Geerts SO, Legrand V, Charpentier J. Further evidence of the association between periodontal conditions and coronary artery disease. *J Periodontol.* 2004;75(9):1274-1280.
33. Ridker PM, Rifai N, Rose L, et al. Comparison of c-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* 2002;347(20):1557-1565.
34. Mattila K, Vesanen M, Valtonen V, et al. Effect of treating periodontitis on c-reactive protein levels: a pilot study. *BMC Infect Dis.* 2002;2:30-32.
35. Slade GD, Ghezzi EM, Heiss G, et al. Relationship between periodontal disease and c-reactive protein among adults in the Atherosclerosis Risk in Communities Study. *Arch Intern Med.* 2003;163(10):1172-1179.
36. Nishimura F, Iwamoto Y, Mineshiba J, et al. Periodontal disease and diabetes mellitus: the role of tumor necrosis factor-α in a 2-way relationship. *J Periodontol.* 2003;74(1):97-102.
37. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion. Behavioral Risk Factor Surveillance System: Prevalence Data. Nov 2005. Available at: http://apps.nccd.cdc.gov/brfss/. Accessed Dec 11, 2005.
38. Barker DJ, Osmond C, Forsén TJ, et al. Trajectories of growth among children who have coronary events as adults. *N Engl J Med.* 2005;353(17):1802-1809.
39. Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged and older adults. *J Periodontol.* 2003;74(5):610-615.
40. Angeli F, Verdecchia P, Pellegrino C, et al. Association between periodontal disease and left ventricular mass in essential hypertension. *Hypertension.* 2003;41(3):488-492.
41. Glick M. Screening for traditional risk factors for cardiovascular disease: a review for oral health-care providers. *J Am Dent Assoc.* 2002;133(3):291-300. Erratum in: *J Am Dent Assoc.* 2002;133(5):560.
42. Cobb CM, Callan DP. Flashpoint in periodontics: patient referral. *Triage.* 2005;1(2):12-16.
43. Bazile A, Bissada N, Nair R, et al. Periodontal assessment of patients undergoing angioplasty for treatment of coronary artery disease. *J Periodontol.* 2002;73(6):631-636.
44. Kuramitsu HK, Kang IC, Qi M. Interactions of *Porphyromonas gingivalis* with host cells: implications for cardiovascular diseases. *J Periodontol.* 2003;74(1):85-89.
45. Miyakawa H, Honma K, Qi M, et al. Interaction of *Porphyromonas gingivalis* with low-density lipoproteins: implications for a role for periodontitis in atherosclerosis. *J Periodontol Res.* 2004;39(1);1-9.
46. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic c-reactive protein level. *J Periodontol.* 2001;72(9):1221-1227.
47. Engebretson SP, Lamster IB, Elkind MS, et al. Radiographic measures of chronic periodontitis and carotid artery plaque. *Stroke.* 2005;36(3):561-566.
48. University of Michigan. The University Record online. Saliva test may spot gum and heart disease. http://www.umich.edu/~urecord/0405/Mar14_05/11.shtml. Accessed Dec 10, 2005.

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AHEAD OF THE CURVE

Frank Formica, DDS
Bowie, MD

Patients in his community near Baltimore and Annapolis consider Dr. Frank Formica the authority in technical dentistry, including temporomandibular joint disturbances. Formica is also respected for providing excellent restorative dentistry and periodontal treatment. Much has changed during his 40-year career, but Formica acknowledges that implementing periodontal medicine is not new; he has been applying credible research findings related to the systemic effects of periodontal disease into his clinical protocols for many years.

Formica believes dentistry is a specialized field of medicine, and that dentists must be aware of new findings in medicine as these findings may directly relate to treatment. He cites articles published during the past 10 years in both dental and medical journals as being pivotal in convincing him to start talking with periodontal patients about their increased risk for cardiovascular diseases (CVD). Formica discusses this research with patients — specifically that heart attacks may be caused from infections such as periodontal disease.

"As a dentist with the knowledge that one of the most common infections of mankind is periodontal disease, I started to order a high sensitivity c-reactive protein (hsCRP) test on patients with the disease," Formica said. HsCRP is a blood test used to identify candidates who are at greater risk for an acute coronary event. Concerned about the role of chronic periodontal infection in increasing patients' risk for CVD, Formica has ordered hsCRP testing on many of his patients during the past five years. He shares the results with physicians, who have been helpful and willing to consult on the medical aspects of treatment.

"A patient related to me that after having had a heart attack, he asked his physician why the attack occurred," Formica said. "The physician was unable to provide a clear explanation to this patient because he had no classic risk factors for cardiovascular disease. When the patient presented to my practice, we diagnosed him with chronic periodontitis. His physician was elated that a risk factor for CVD had been identified and treated."

"In another case, a long-term patient with periodontal disease who refused treatment despite repeated warning of dangers of untreated periodontal disease, suffered a heart attack. The progress notes recorded over the years document the diagnosis of periodontal disease and subsequent

This column is dedicated to clinicians, educators, and researchers at the forefront of oral-systemic medicine. To call them early adopters is an understatement. Professionals who are ahead of the curve read the research and look for appropriate, innovative opportunities to transfer the research to private practices or academic settings. Pursuits for excellence fuel their purposes, plans, and searches for better ways to take care of patients and motivate students. To those ahead of the curve, PennWell says, "Well done."

Stories welcome: To contribute stories about other clinicians, educators, and researchers at the forefront of oral-systemic medicine, please e-mail Casey Hein, Chief Editor, at caseyh@pennwell.com.

A complimentary copy of this article may be downloaded in Adobe Acrobat at www.thesystemiclink.com

recommendations for treatment. The last entry was, 'This patient will have a heart attack,' and six months later he suffered his first episode of myocardial infarction."

Formica was asked what he thinks is the most needed change in educating dentists and physicians. The most important change he would make in achieving interdisciplinary education would be to add a course in internal medicine for dental students and a course in oral medicine for medical students so physicians would have the diagnostic knowledge necessary to refer to dentists those patients at risk for oral diseases and conditions.

When asked what he thought researchers will have discovered about the relationship between the oral cavity and the whole body in 20 years, Formica said, "The mouth mirrors what is happening in the body, and it can be an entry point for infections. The treatment of periodontal disease must be both local and systemic" (F. Formica, written communication, Nov 2005).

Jonathan Richter, DDS
Lauren Kilmeade, RDH
Great Neck, NY

Dr. Jonathan Richter and Lauren Kilmeade share a vision for building a practice totally dedicated to comprehensive periodontal medicine. Their dedication was jump started in part by the death of Kilmeade's 59-year-old father, who died from heart disease and diabetes in 2001.

At the heart of their comprehensive wellness model is Kilmeade teaching patients how oral health affects overall systemic health. They credit dental assistants — one of whom is a licensed practical nurse — and members of the business staff for their knowledge of oral-systemic medicine and their ability to reinforce patient education.

Clinical protocols in Richter's office include monitoring blood pressure at all recare appointments, using glucometers to monitor diabetic patients' blood sugar before procedures, and using chairside HbA1c analyzers to screen patients for undiagnosed diabetes and to determine whether periodontal treatment was effective in reducing patients' glycosylated hemoglobin.

Richter communicates with patients' physicians (endocrinologists, cardiologists, rheumatologists, obstetricians, and internists) to discuss specific cases and growing evidence to support periodontal systemic links. In addition, Richter is diligent about monitoring clinical endpoints that give him the information to more accurately refer to medical specialists those patients who do not respond favorably to periodontal treatment.

Richter and Kilmeade promote smoking cessation by providing relevant literature and recommending specific smoking cessation counselors. They have identified many patients who were at risk for diabetes and who later were confirmed diabetics upon evaluation by their physicians. Some patients credit early intervention of their diabetes to Richter and Kilmeade.

Richter and Kilmeade have organized round table discussions with members of the medical community. The intent is to share ideas on mutual patient care and foster collaborative relationships.

When asked how members of the medical community have reacted to their progressive diagnostic and treatment philosophies, Richter said, "Initially the medical community thought we were using the HbA1C to diagnose. When they realized how we were utilizing the data to manage and treat our patients comprehensively and to refer them to the proper physicians, they seemed to embrace the concept" (J. Richter, written communication, Nov 2005).

Kilmeade and Richter cite the lack of support from organized dentistry and medicine as a hurdle to the implementation of oral-systemic medicine, but that doesn't seem to have slowed them down.

When asked what patients say about this kind of comprehensive care, Kilmeade said, "Our patients choose us for their dental care because they are confident they are receiving comprehensive quality care that is customized to their individual needs. They indeed participate in helping us help them. Once the oral/systemic concept is presented and applied to their personal health, they are converted into true believers, taking their oral health to heart as much as we do" (L. Kilmeade, written communication, Nov 2005).

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TOOLS FOR IMPLEMENTATION

Helping Patients Understand the Suspected Link Between Gum Disease and Heart Attack/Stroke

As your health-care providers, we believe that patient education is one of the best ways we can help you stay healthy. Therefore, we would like to share with you that there is a growing body of research that suggests that infection from the oral cavity may increase the risk and complications for a number of serious diseases and conditions. Heart disease and stroke are among these. Although this research is relatively new and there are a number of questions which remain unanswered at this time, it does appear that there may be a link between gum disease and increased risk for heart disease and stroke. Research to better understand the relationship between gum disease and cardiovascular diseases such as heart disease and stroke is currently underway. While we wait for the findings of this research, it is important to point out the risk factors for heart disease and stroke which medical research has already identified.

What are the most highly recognized risk factors for heart disease or stroke?

The American Heart Association has identified certain factors that increase the risk of heart and blood vessel diseases. These include the following:[1]

- Increasing age
- Family history of premature coronary artery disease
- High blood pressure
- Low HDL cholesterol
- Obesity and overweight
- African American ethnicity
- Alcohol
- Male gender
- Tobacco smoke
- High LDL cholesterol
- Diabetes
- Physical inactivity
- Stress

It has been estimated that each year 250,000 sudden deaths from coronary heart disease occur before the victim reaches the hospital. For many of these victims there was no previous recognition of cardiovascular diseases;[2] therefore, it is extremely important that you discuss these risk factors and your specific risk profile with your medical care provider. It is also significant that of the 1.5 million heart attacks and 600,000 strokes that occur in the U.S. each year, almost half will affect people who appear to be healthy with normal or low cholesterol levels.[3] As a result, scientists are now searching for other risk factors for heart disease and stroke. Whether gum disease is categorized as a risk factor for heart disease and stroke remains undetermined at this time. So what do we already know about how gum infections may affect cardiovascular health?

How might gum disease affect cardiovascular health?

Diseases of the heart and blood vessels are most commonly related to thickening of the walls of arteries, a condition called atherosclerosis. It is believed that atherosclerosis results from damage to the artery wall that, in turn, results from inflammation within the artery wall along with deposits of fat. The combination of fat deposits and artery wall inflammation leads to the development of an "atheroma" or plaque.

Part of this inflammatory damage is from infections of various sources. Many researchers believe that bacteria from gum infections (illustrated in circle 1) could be one of the infec-

tions involved with this injury to the arter
that allows the bacteria to enter the bloo
gums bleed, a path for bacteria to enter
through blood vessels to distant sites in
artery becomes less elastic and the inside
in circle 2). What happens next is small bl
get clogged which causes blood flow to be
ing on the location of the blood clot. The
of research which is under investigation
recognize the following warning signs of

What are the warning signs of gum disease?

- Gums that bleed during brushing or eating
- Increased space that starts to develop between teeth
- Gums that feel swollen or tender
- Gums that are receding (pulling back from your teeth)
- Persistent bad breath
- Pus between your teeth and gums
- Changes in the way your teeth fit together when you bite
- Sores in your mouth

You should discuss warning signs of gum disease and risk factors for heart disease with your dental- and medical-care providers, and it is recommended that adults be evaluated by their dentist or dental hygienist for periodontal disease. More information about gum disease and its relationship to cardiovascular disease may be found on the Web site of the American Academy of Periodontology, which may be accessed at www.perio.org. More information on heart disease and stroke may be accessed from the American Heart Association at www.americanheart.org; the National Heart, Lung and Blood Institute at www.nhlbi.nih.gov/index.htm; and from the American College of Cardiology at www.acc.org.

References

1. American Heart Association. Risk factors and coronary heart disease. Available at: http://www.americanheart.org/presenter.jhtml?identifier=500. Accessed Dec 13, 2005.
2. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Division of Adult and Community Health. Cardiovascular Health: A Public Health Action Plan to Prevent Heart Disease and Stroke. Section 1. Heart Disease and Stroke Prevention: Time for Action. Myths and Misconceptions. June 2005. Available at: http://www.cdc.gov/cvh/Action_Plan/full_sec1_myths.htm. Accessed Dec 11, 2005. Page. C-reactive protein: A simple test to help predict risk of heart attack and stroke.
3. Bibbo PM. Cardiology Patient Page. 2003;108(12):e81-e85.
4. American Academy of Periodontology. Take a self-evaluation quiz. Available at: http://www.perio.org/consumer/4a.html. Accessed Dec. 12, 2005.

As a courtesy to the profession, *Grand Rounds in Oral-Systemic Medicine*™ has designed patient education materials to assist health-care providers in talking with patients about the relationship between oral disease and overall health.

To download a file of this patient education information, go to:

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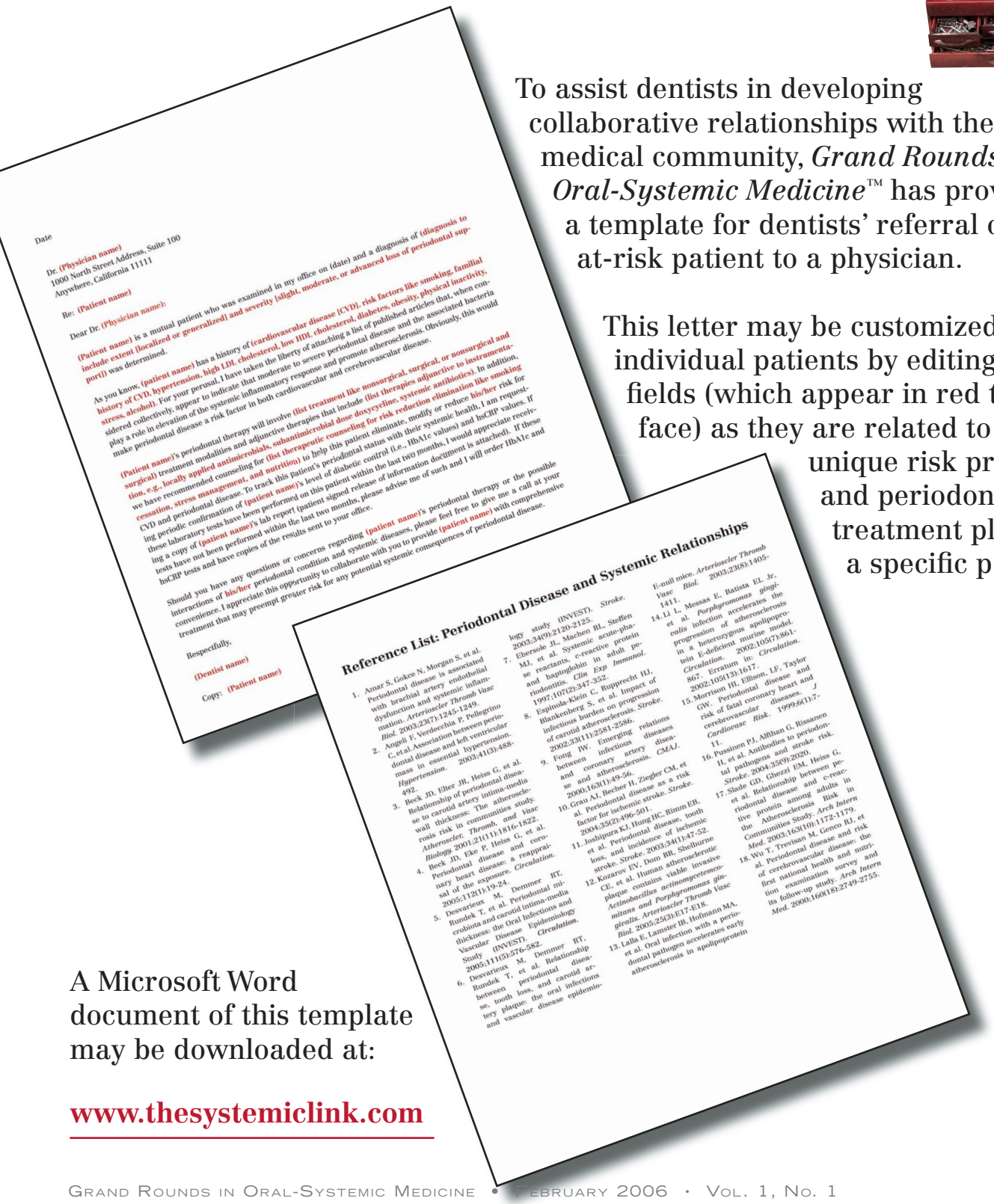
TOOLS FOR IMPLEMENTATION

To assist dentists in developing collaborative relationships with the medical community, *Grand Rounds in Oral-Systemic Medicine*™ has provided a template for dentists' referral of an at-risk patient to a physician.

This letter may be customized for individual patients by editing the fields (which appear in red typeface) as they are related to the unique risk profile and periodontal treatment plan of a specific patient.



Date

Dr. (Physician name)
1000 North Street Address, Suite 100
Anywhere, California 11111

Re: (Patient name)

Dear Dr. (Physician name):

(Patient name) is a mutual patient who was examined in my office on (date) and a diagnosis of (diagnosis to include extent (localized or generalized) and severity (slight, moderate, or advanced loss of periodontal support)) was determined.

As you know, (patient name) has a history of (cardiovascular disease (CVD), risk factors like smoking, familial history of CVD, hypertension, high LDL cholesterol, low HDL cholesterol, diabetes, obesity, physical inactivity, stress, alcohol). For your perusal, I have taken the liberty of attaching a list of published articles that, when considered collectively, appear to indicate that moderate to severe periodontal disease and the associated bacteria play a role in elevation of the systemic inflammatory response and promote atherosclerosis. Obviously, this would make periodontal disease a risk factor in both cardiovascular and cerebrovascular disease.

(Patient name)'s periodontal therapy will involve (list treatment like nonsurgical, surgical, or nonsurgical and surgical) treatment modalities and adjunctive therapies that include (list therapies adjunctive to instrumentation, e.g., locally applied antimicrobials, subantimicrobial dose doxycycline, systemic antibiotics). In addition, we have recommended counseling for (list therapeutic counseling for risk reduction elimination like smoking cessation, stress management, and nutrition) to help this patient eliminate, modify or reduce his/her risk for CVD and periodontal disease. To track this patient's periodontal status with their systemic health, I am requesting periodic confirmation of (patient name)'s level of diabetic control (i.e., HbA1c values) and hsCRP values. If these laboratory tests have been performed on this patient within the last two months, I would appreciate receiving a copy of (patient name)'s lab report (patient signed release of information document is attached). If these tests have not been performed within the last two months, please advise me of such and I will order HbA1c and hsCRP tests and have copies of the results sent to your office.

Should you have any questions or concerns regarding (patient name)'s periodontal therapy or the possible interactions of his/her periodontal condition and systemic diseases, please feel free to give me a call at your convenience. I appreciate this opportunity to collaborate with you to provide (patient name) with comprehensive treatment that may preempt greater risk for any potential systemic consequences of periodontal disease.

Respectfully,

(Dentist name)

Copy: (Patient name)

Reference List: Periodontal Disease and Systemic Relationships

1. Amar S, Gokce N, Morgan S, et al. Periodontal disease is associated with brachial artery endothelial dysfunction and systemic inflammation. *Arterioscler Thromb Vasc Biol.* 2003;23(7):1245-1249.
2. Angeli F, Verdecchia P, Pellegrino C, et al. Association between periodontal disease and left ventricular mass in essential hypertension. *Hypertension.* 2003;41(3):488-492.
3. Beck JD, Elter JR, Heiss G, et al. Relationship of periodontal disease to carotid artery intima-media wall thickness: The atherosclerosis risk in communities study. *Atherosclerc. Thromb. and Vasc Biology.* 2001;21(11):1816-1822.
4. Beck JD, Eke P, Heiss G, et al. Periodontal disease and coronary heart disease: a reappraisal of the exposure. *Circulation.* 2005;112(1):19-24.
5. Desvarieux M, Demmer RT, Rundek T, et al. Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation.* 2005;111(5):576-582.
6. Desvarieux M, Demmer RT, Rundek T, et al. Relationship between periodontal disease, tooth loss, and carotid artery plaque: the oral infections and vascular disease epidemiology study (INVEST). *Stroke.* 2003;34(9):2120-2125.
7. Ebersole JL, Machen RL, Steffen MJ, et al. Systemic acute-phase reactants, c-reactive protein and haptoglobin in adult periodontitis. *Clin Exp Immunol.* 1997;107(2):347-352.
8. Espinola-Klein C, Rupprecht HJ, Blankenberg S, et al. Impact of infectious burden on progression of carotid atherosclerosis. *Stroke.* 2002;33(11):2581-2586.
9. Fong IW. Emerging relations between infectious diseases and coronary artery disease and atherosclerosis. *CMAJ.* 2000;163(1):49-56.
10. Grau AJ, Becher H, Ziegler CM, et al. Periodontal disease as a risk factor for ischemic stroke. *Stroke.* 2004;35(2):496-501.
11. Joshipura KJ, Hung HC, Rimm EB, et al. Periodontal disease, tooth loss, and incidence of ischemic stroke. *Stroke.* 2003;34(1):47-52.
12. Kozarov EV, Dorn BR, Shelburne CE, et al. Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Arterioscler Thromb Vasc Biol.* 2005;25(3):E17-E18.
13. Lalla E, Lamster IB, Hofmann MA, et al. Oral infection with a periodontal pathogen accelerates early atherosclerosis in apolipoprotein E-null mice. *Arterioscler Thromb Vasc Biol.* 2003;23(8):1405-1411.
14. Li L, Messas E, Batista EL, Jr., et al. *Porphyromonas gingivalis* infection accelerates the progression of atherosclerosis in a heterozygous apolipoprotein E-deficient murine model. *Circulation.* 2002;105(7):861-867. Erratum in: *Circulation.* 2002;105(13):1617.
15. Morrison HI, Ellison LF, Taylor GW. Periodontal disease and risk of fatal coronary heart and cerebrovascular diseases. *J Cardiovasc Risk.* 1999;6(1):7-11.
16. Pussinen PJ, Alfthan G, Rissanen H, et al. Antibodies to periodontal pathogens and stroke risk. *Stroke.* 2004;35(9):2020.
17. Slade GD, Ghezzi EM, Heiss G, et al. Relationship between periodontal disease and c-reactive protein among adults in the Atherosclerosis Risk in Communities Study. *Arch Intern Med.* 2003;163(10):1172-1179.
18. Wu T, Trevisan M, Genco RJ, et al. Periodontal disease and risk of cerebrovascular disease: the first national health and nutrition examination survey and its follow-up study. *Arch Intern Med.* 2000;160(18):2749-2755.

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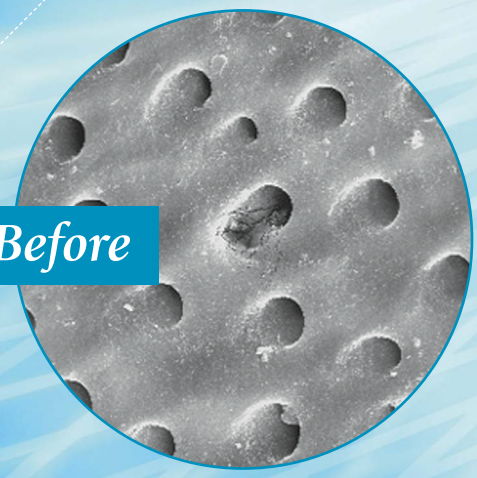

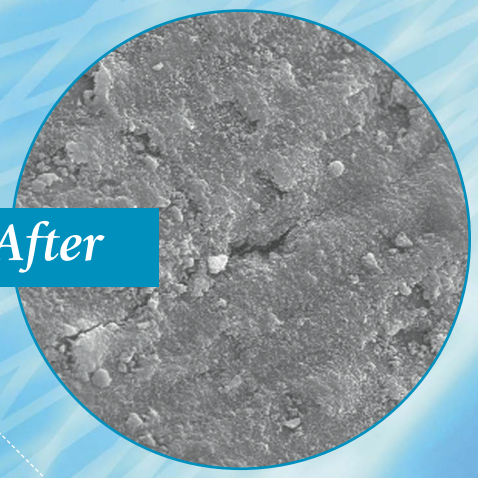

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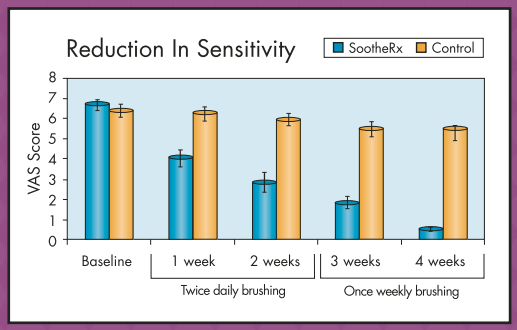

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