HHS Public Access

Author manuscript

J Stroke Cerebrovasc Dis. Author manuscript; available in PMC 2017 October 02.

Published in final edited form as:

J Stroke Cerebrovasc Dis. 2013 November ; 22(8): 1420–1427. doi:10.1016/j.jstrokecerebrovasdis.2013.06.024.

Periodontal Disease and Recurrent Vascular Events in Stroke/TIA Patients

Souvik Sen[*,†], **Roxanne Sumner**[†], **James Hardin**[†], **Silvana Barros**[‡], **Kevin Moss**[‡], **James Beck**[‡], and **Steven Offenbacher**[‡]

[*]Department of Neurology, University of North Carolina, Chapel Hill, North Carolina

[†]University of South Carolina, Columbia, South Carolina

[‡]Department of Periodontology, University of North Carolina, Chapel Hill, North Carolina

Abstract

Periodontal disease has been shown to be associated with incident stroke. We investigated whether periodontal disease is independently associated with recurrent vascular events and certain inflammatory markers in stroke/TIA patients. In this prospective longitudinal hospital-based cohort study, periodontal disease was assessed in stroke/TIA patients. High periodontal disease was defined as the highest tertile of extent (% of sites) with attachment loss ≥ 5 mm. Serum interleukin-6, high sensitivity C-reactive protein and soluble intracellular adhesion molecule-1 were measured. The patients were followed for recurrent vascular events-stroke, TIA, myocardial infarction and vascular death. In the 106 patients that were evaluated, 40 (38%) showed high periodontal disease and 27 (26%) had recurrent vascular events over a median of 24 months (range 12–24 months). High periodontal disease patients had higher levels of interleukin-6 (p=0.01) and soluble intracellular adhesion molecule-1 (p=0.03). High periodontal disease was associated with recurrent vascular events before (Log rank p=0.01, hazard ratio 2.6, 95% CI, 1.2–5.7) and after adjustment for significant confounders -age and stroke status (Hazard Ratio 2.5, 95% confidence interval, 1.1 to 5.5, p=0.03); adjustment for possible confounders age, males, years of education and cardioembolic strokes (hazard ratio 2.8, 95% confidence interval, 1.2–6.5, p=0.02); and adjustment for propensity score that accounted for all potential measured confounders (hazard ratio 2.8, 95% confidence interval,1.2–6.5, p=0.02). There is an independent association between high periodontal disease and recurrent vascular events in stroke/TIA patients. High periodontal disease is also associated with higher serum levels of interleukin-6 and soluble intracellular adhesion molecule-1.

Corresponding author: Souvik Sen MD, MS, MPH, FAHA, Professor and Chair, Dept. of Neurology, University of South Carolina School of Medicine, 8 Medical Park, Suite 420, Columbia, SC 29203, USA, Tel: (803) 545-6073, Souvik.Sen@uscmed.sc.edu.
Research site: Departments of Neurology and Periodontology, University of North Carolina, Chapel Hill, North Carolina, USA

INTRODUCTION

Periodontal disease (PD) is present in approximately 40% of the adult population in the United States.[1] Post-hoc analyses of prospective-longitudinal studies and smaller case-control studies have reported an association between PD and incident stroke.[2] These studies show that PD appears to bear a stronger association with stroke than coronary artery disease (CAD).[3] In a combined analysis of two prospective studies, PD was found to increase the risk of incident stroke nearly three-fold.[4] Recently, a case control study confirmed the independent graded association between the severity of PD and the risk of incident stroke.[5] In the present study, we investigated the effect of high periodontal disease (HPD) on recurrent vascular events in ischemic stroke/transient ischemic attack (TIA) patients. A recent prospective study found an association between inflammatory markers, with recurrent vascular events in stroke/TIA patients.[6] PD has been postulated to be a result of a complex interplay of infection, immune and resulting inflammatory response.[7] A growing body of evidence suggests that infections, and associated inflammatory markers may be emerging as potentially modifiable stroke risk factors.[8] Therefore, the associations between PD and inflammatory markers with recurrent vascular events were investigated.

PATIENTS AND METHODS

In this prospective, longitudinal, hospital-based cohort study, consecutive patients admitted with stroke/TIA were screened for eligibility. All patients had risk factors assessed, and were classified into etiological stroke subtypes. A brain CT/MRI was used to detect cerebral ischemia as well as exclude intracerebral and subarachnoid hemorrhage. Other exclusion criteria included: age <18 years, coma, conditions limiting life expectancy to <12 months, having <5 teeth (PD assessment unreliable), recent infection and/or antibiotic use (within 30 days). The study was approved by the local Institutional Review Board and a written informed consent was obtained prior to study participation. Enrolled patients underwent protocol-mandated assessments for PD, serum inflammatory markers and follow-up for recurrent vascular events.

PD Assessments

The dental examiners calibrated against a standard examiner, as well as each other for measures of PD. These dental examiners were not involved in medical chart review, consenting, clinical data collection and were intentionally uninformed as to the subject's stroke information to avoid potential measurement bias. At the end of their examination, patients were advised in writing as to their periodontal status but were not referred for care to avoid follow-up bias. Specifically, the PD assessment included measurements of probing pocket depth and gingival recession on six sites for all teeth using a UNC-12 periodontal probe rounded to the next lower whole millimeter. Attachment level (AL), which is a valid measure of historical periodontal destruction,[9] was calculated from the sum of pocket depth and gingival recession scores. Extent of PD was derived from percentage of sites with AL ≥ 5 mm. Corrections were made to adjust for the fact that buccal sites often exhibit AL that consists primarily of gingival recession from causes not related to periodontitis.[10] Based on the extent of AL ≥ 5 mm, subjects were divided into those with low periodontal disease

(LPD) (lower two tertiles with extent of attachment loss <1.3%) and those with HPD (highest tertile with extent of AL ≥ 1.3%). Our previous work has indicated that mild periodontitis is unlikely to have any systemic effects or influence on clinical outcome; further, our previous research has indicated evidence that more extensive infection is needed for periodontitis to affect vascular risk.[10] It is important to have a referent group with little or no periodontal disease, rather than comparing the "cases" to a group that included individuals with moderate levels of disease. Stroke/TIA predominantly affects older population (50 years and older), in whom an estimated third have severe periodontitis.[11] Based on this consideration we selected *a priori*, the cutoff using highest tertile, to capture the severe periodontitis subjects and yet also provide adequate sample size in each cell. To investigate the measure, correlations between extent of AL ≥ 5 mm and other measures of PD[12] (mean pocket depth, extent pocket depth ≥ 4mm, mean attachment loss, extent attachment loss ≥ 3 mm, extent plaque score ≥ 1, extent gingival index ≥1 and extent bleeding on probing) were assessed and showed good distinction of the groups in terms of association with the outcome.

Clinical Definitions

Stroke and stroke risk factors were defined based on previously described criteria.[13] Stroke risk factors, laboratory assessments and stroke subtype were assessed at the time of initial qualifying event (stroke/TIA). TIA was defined as brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction.[14] Myocardial Infarction (MI) was defined according to criteria modified from the 2000 Consensus Conference of the European and American Colleges of Cardiology.[15] Vascular death was defined as death ≤ 30 days from stroke/MI, where other causes of death had been excluded, or a sudden death from unexplained cause(s).

Laboratory measurements

From samples taken at enrollment, patients were assessed for the following inflammatory markers: serum interleukin-6 (IL-6), high sensitivity C-reactive protein (hs-CRP) and soluble intracellular adhesion molecule-1 (s-ICAM). Serum levels of s-ICAM and IL-6 were determined using commercial ELISA assay kits, and hs-CRP was determined with FMAP multiplex assay on a BioPlex 200 system. Reagents for assays were from R&D Systems (Minneapolis, MN). Patients receiving antibiotics for infection at the time of enrollment were excluded (N=1). Other causes of inflammation or chronic inflammatory disease were ruled out by screening the Atherosclerosis Risk in Communities (ARIC) inflammation form, administered at enrollment.[16]

Assessment of Stroke Etiology, Stroke Severity and TIA symptoms

Ischemic stroke etiology was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[17] The initial ischemic stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS) performed on presentation to the hospital by qualified personnel. All TIAs were assessed by diffusion weighted image to rule out ischemic stroke.[18] Additionally, in patients in whom the diagnosis of TIA was related to cerebral ischemia, $ABCD^2$ score was assessed to determine if the patients were likely to be experiencing a true TIA.[19]

Follow-up

Follow-up phone calls were conducted at 6-month intervals for a median of 24 months from enrollment for vascular events including stroke, MI and death. During follow-up phone-calls, patients were asked about hospitalization occurring, occurrence of MI or recurrent stroke/TIA. For patients with outcome events, the clinical records were reviewed for confirmation. Date and cause of death were recorded for patients who died during the study. The recurrent vascular event was adjudicated by investigators, who were blinded to the PD status.

Statistical analysis

Statistical analysis was performed using SAS version 9.2 (SAS institute, Cary, NC) and Stata version 12.0 (Stata Corporation, College Station, TX). All normally distributed continuous variables are reported as mean ± standard deviation and compared using t-tests. Non-normally distributed continuous variables are depicted as median (inter-quartile range) and compared using Mann-Whitney U-test. All categorical variables are reported as proportions and inter-group difference was assessed by the χ^2 test. Initially, the cumulative event-free rates for the time to composite vascular events (stroke, TIA, MI and vascular death) were estimated by Kaplan-Meier product limit method and the two groups, those with HPD and those with LPD, compared by the log-rank test. Subsequently, Cox proportional hazards analysis was used to identify risk factors for composite vascular events after adjusting for significant confounders using methods discussed below. Complete exposure (periodontal status) and outcome (recurrent vascular event) was available in all 106 enrolled subjects. Missing data in the laboratory parameters (4%) were replaced with the mean for the cohort for univariate and multivariable analyses.

Covariates assessed for confounding included stroke risk factors, laboratory parameters known to be associated with stroke risk (low-density lipoprotein [LDL], high-density lipoprotein [HDL] and homocysteine levels), and stroke subtypes. The covariates assessed for confounding also included those that were found to confound the association between PD and stroke in prior studies[2–4] and included age, gender, race, hypertension, diabetes, hypercholesterolemia, body mass index (BMI), CAD, smoking, alcohol use, education level and estimated annual income. Only the covariates that were noted to change the hazards ratio (HR) by ≥ 5% were considered to produce significant confounding and included in Model 1. In Model 2, the covariates included were baseline characteristics that were significantly different (<0.05) among exposure groups. The results in each of these models were expressed as adjusted HRs and corresponding 95% confidence interval (CI). Propensity scores were calculated for each study subject by applying the subject's values to the logistic model.[20] The propensity score reflected each subject's conditional probability of being exposed (HPD) given the confounding variables. The c-statistic for the propensity score model was 0.76, indicating an acceptable discrimination between HPD and LPD groups. The results in each of these models were expressed as adjusted HRs and corresponding 95% CI.

Sample size estimation was based on assumption that stroke/TIA patients have a high rate of composite vascular event as noted in prior studies.[21, 22] With a total sample size of 100 and at least 40 participants in each exposure group, we estimated we would have a 90% power to

detect a 15% difference in composite vascular event (a priori hypothesis) by log-rank test. The two-tailed Type I error rate (alpha) was set at 0.05.

Our data did not include a measure of medical therapy compliance. Non-compliance is associated with PD and also associated with recurrent strokes. An obvious concern is that therapy non-compliance could fully mediate the established effects of PD. As such, we assessed the sensitivity of the HPD results in fitted survival models to the unmeasured confounder of medical noncompliance.[23]

RESULTS

Of the 156 patients that were screened, 110 met all the selection criteria and consented to the study; 106 patients completed a full periodontal examination (mean ± standard deviation = 29±13 days, from index stroke/TIA). The various measures of PD showed significant correlation with the one used to define HPD –highest tertile of subjects with extent of AL ≥ 5 mm (Table 1). Baseline characteristics of the study patients stratified into HPD (N=40) and LPD (N=66) are described in Table 2. Patients with HPD were more likely to be older (p=0.05), males (p=0.03) and have fewer years of education (p=0.007). Stroke patients were more likely to have HPD than TIA patients (42% vs. 25%) although the difference did not reach statistical significance (p=0.11). The proportions of the stroke subtypes appear to be different between HPD and LPD (p=0.03). Specifically, patients with HPD were more likely to have cardioembolic strokes (28% vs. 6%, p=0.02). Although, large artery atherothrombosis was less common in the LPD, the intergroup difference was not statistically significant. In the subset of patients with stroke (N=78) median NIHSS was higher in the HPD group (5) compared to the LPD group (3), although the difference did not reach statistical significance (p=0.07). In the remaining subset of TIA patients (N=28), the median $ABCD^2$ score was higher (p=0.03) in the HPD group (4) compared to the LPD group (3).

The laboratory characteristics including inflammatory markers are outlined in Table 3. There were no significant differences between the HPD and LPD groups in fasting lipid profiles. Mean LDL was greater than 100 mg/dl across both groups, which is the target LDL for secondary stroke prevention.[1] Plasma homocysteine level, although higher in HPD compared to LPD, was not significantly different (p=0.26). Among the inflammatory markers, IL-6 levels (p=0.01) and s-ICAM levels (p=0.04) were significantly higher in the HPD compared to LPD. There were no significant differences between HPD and the LPD in the level of hs-CRP which was elevated for both groups.

Over a median of 24 months from enrollment, 27 patients exhibited vascular events; including, sixteen with cerebrovascular events (9 stroke and 7 TIAs), three MIs, and eight vascular deaths. Sixteen (40%) of the 40 patients with HPD had vascular events; including, nine with cerebrovascular events (5 strokes and 4 TIAs), two MIs and five vascular deaths. Among the 66 patients with LPD, 11 (17%) had vascular events, including seven stroke/TIA, one MI and three vascular deaths over the same period of follow-up. There was a significant difference in cumulative event-free survival between the HPD group (mean survival 2.1 years, 95% CI 1.6–2.5 years) and LPD group (mean survival 2.7 year, 95% CI 2.4–2.9

years). The two distributions were significantly different according to log-rank testing (p=0.01) and are depicted in the Kaplan-Meier survival curve (Figure 1). Among all the covariates, only age and stroke status significantly confounded the PD and composite vascular outcome association. After adjustment for these confounders, association between PD and composite vascular events, remained significant (HR 2.5, 95% CI, 1.1 to 5.5, p=0.03, Table 4). As noted above, stroke/TIA patients with HPD were older, had higher proportion of males, fewer years of education and higher rates of cardioembolic strokes (Table 2). After adjustment for these covariates, association between PD and composite vascular events, remained significant (HR 2.8, 95% CI, 1.2 to 6.5, p=0.02, Table 4). Multivariable Cox regression showed HPD was also associated with composite vascular events, after adjustment for propensity score (HR 2.8, 95% CI 1.2 – 6.5, p = 0.02, Table 4).

The sensitivity of the HPD results in fitted survival models to the unmeasured confounder of medical noncompliance is shown in Table 5.[23] To fully mediate the association of HPD, medication non-compliance must have a hazard ratio of at least 1.3 where noncompliance was 1.75 times as likely (70%/40%) among the HPD patient.

DISCUSSION

Our findings indicate that in stroke/TIA patients, HPD is independently associated with an increased risk of recurrent vascular events. The Kaplan-Meier plots (Figure 1) suggest significant separation of survival curves in the HPD and LPD patient groups, at and beyond six months from the periodontal assessment.

To our knowledge, we are one of the first to report an association between PD and recurrent vascular events in a stroke/TIA population. In the past, at least four case-control and three cohort studies have reported a major positive association between PD and ischemic stroke, in stroke-free populations[24] with similar reported effect size. The mechanisms by which periodontitis may contribute to ischemic stroke have recently been reviewed.[25] The proposed mechanisms include inflammation-mediated procoagulant state, atherosclerosis mediated by direct microbial invasion of blood vessel wall as well as systemic inflammatory markers, and interaction with vascular risk factors.

The association between PD and cardiovascular disease is well established;[2] however, the link between PD and ischemic stroke has only recently been explored. A recent meta-analysis did not find evidence to support a causal association between PD and stroke (ischemic and hemorrhagic strokes combined).[26] Hemorrhagic stroke, however, is pathophysiologically distinct from ischemic stroke in the fact that it is unrelated to atherosclerosis. Eliminating the studies that included hemorrhagic strokes, there are two cohorts, two case-controls and one cross sectional study(s) that have specifically looked at ischemic stroke as the sole dependent variable.[25] All of these studies show significant association between PD and ischemic stroke. The most powerful evidence, in humans, for a mechanism which links PD with ischemic stroke is the isolation of dental pathogenic bacteria within carotid plaque[27] and the association between serological markers of dental pathogen with carotid intimal medial thickness.[10] A recent case-control study found an association between the antibody to Porphyromonas gingivalis, with carotid atherosclerosis

and atrial fibrillation.[28] Since atrial fibrillation is a common reason for cardioembolic stroke, our results which found a significant association between HPD and cardioembolic stroke, is not surprising (Table 1).

We found a significant association between HPD and levels of serum inflammatory markers, namely IL-6 and s-ICAM. The nidus that leads to a downstream increase in s-ICAM is IL-6. Further, IL-6 is also a potent inducer of CRP release which has been suggested to directly alter vascular integrity; thus, promoting atherogenesis.[29] We, however, also found consistently high hs-CRP values across both groups with no statistical difference. This finding may be explained by the fact that both HPD and LPD groups included stroke/TIA subjects with high prevalence of stroke risk factors. As noted by others, this finding is also consistent with the hypothesis that the association between CRP levels and stroke can be explained by the patient's age and risk factors.[30]

Finally, our results show study participants whom had less years of education were more likely to have HPD. This finding is consistent with a recent case-control study that found education was an important contributor to the stroke risk associated with lower socioeconomic status.[31] Further, two meta-analyses, have shown that patients with low educational attainment are at a greater risk of developing PD[32] and stroke; regardless, of traditional risk factors.[33] Less education, may contribute to poor care and compliance of stroke risk factors and dental care.

This study has a few limitations. First, generalisability may be limited by the requirement that stroke/TIA patients agreeing to have PD assessments. Second, the sample size of the study, although powered to test the primary hypothesis, is inadequate to test the association within subgroups such as TIA or the individual stroke subtypes. Third, elevated hs-CRP could have been attributable to another underlying infectious process; however, this possibility is unlikely as all participants were screened for recent antibiotic use or illness. Furthermore, intensive periodontal therapy has been shown to improve patients' vascular risk factor profile.[34] In a randomized study involving severe periodontitis patients, intensive periodontal therapy led to an improvement in endothelial function, hinting that aspects of periodontitis-associated inflammation and vascular injury might be reversible.[35] Results of a recently published population-based study in Taiwan suggests that maintenance of periodontal health by dental prophylaxis and PD treatment can help reduce the incidence of ischemic stroke.[36, 37] Further studies are needed to assess whether PD treatment can lead to reduction in serum inflammatory markers and prevent recurrent vascular events in stroke/TIA patients. Finally, we did not measure medical therapy non-compliance, known to adversely impacts outcomes in stroke/TIA patients.[38]

To address the issue of medical therapy non-compliance, an unmeasured confounder, we conducted a sensitivity analysis to test its effect on the association between HPD and recurrent vascular events. To fully mediate the association of HPD, medication non-compliance must have a hazard ratio of at least 1.3 where noncompliance was 1.75 times as likely (70%/40%) among the HPD patient. Based on reported rate of non-compliance of approximately a third of stroke/TIA patients,[38] this scenario is less likely.

Internal validity of the model was tested by taking repeated bootstrap samples (with replacement) from the original data, models are estimated using a backward stepwise procedure.[39] The final list of predictors is comprised of those predictors which were retained in a high proportion of the models (> 60%). A future study is needed to test external validity.

In conclusion, we found that PD is associated with recurrent vascular events in stroke/TIA patients. We also found an association between PD and inflammatory markers, namely IL-6 and s-ICAM. Further studies are needed to examine if treatment of HPD can result in lower levels of inflammatory markers and a lower rate of recurrent vascular events in stroke/TIA patients.

Acknowledgments

Study funding: Mid-Atlantic Affiliate of the American Heart Association grant-in-aid 0755464U and NIH grants M01RR00046, ULTR000083 and UL1RR025747

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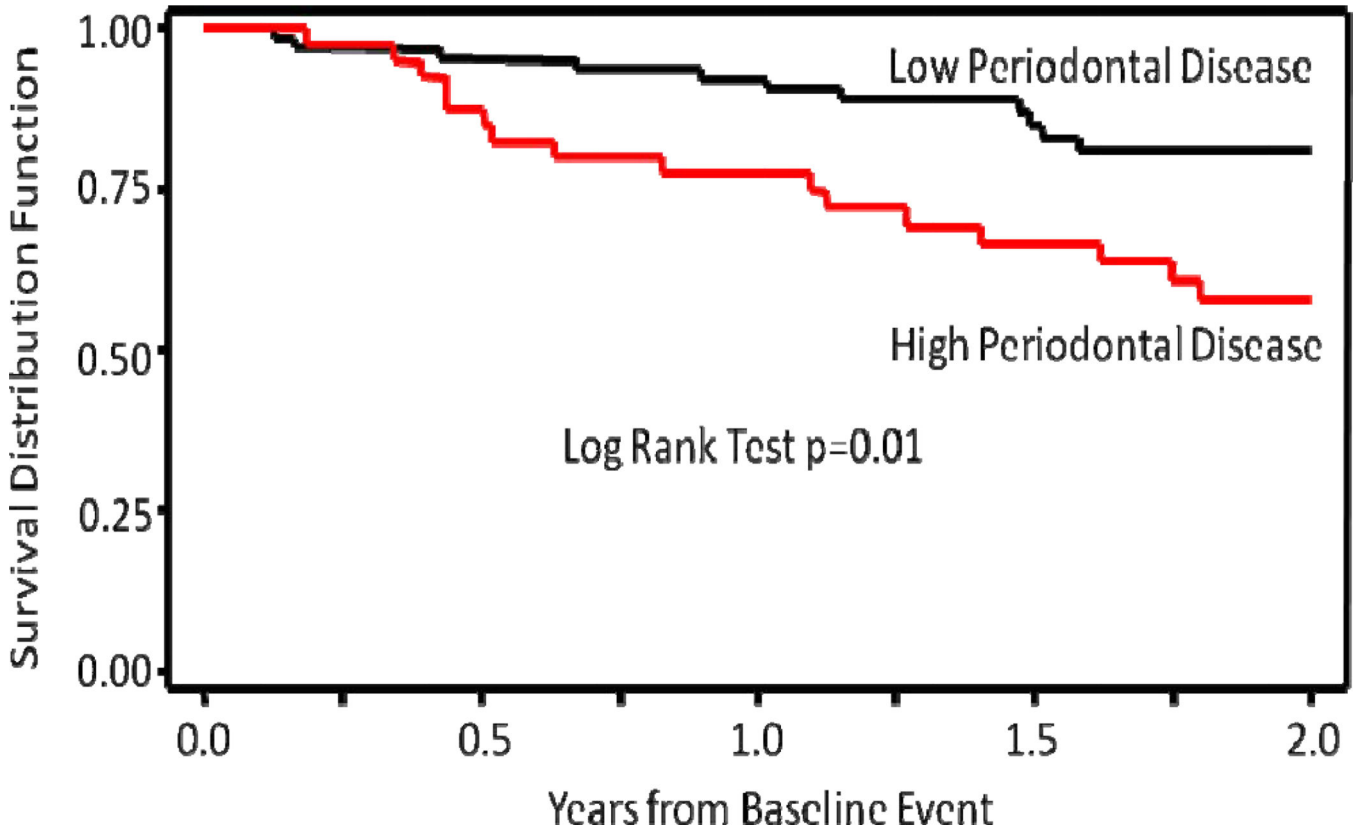

Figure 1.
Kaplan-Meier Survival Functions: Differences for Stroke/TIA Patients with Low versus High Periodontal Disease.

Table 1

The correlation of various measures of periodontal disease with the upper quartile of extent of attachment loss ≥5 mm.

	Extent of attachment loss ≥5mm		
	Upper Tertile N=40	**Lower 2 Tertiles N=66**	**p-value**
Mean Pocket Depth	2.41 (0.62)	1.92 (0.35)	<0.0001
Extent Pocket Depth ≥4mm	15.7 (14.5)	4.93 (6.55)	<0.0001
Mean Attachment Loss (Interproximal)	2.48 (0.98)	1.30 (0.38)	<0.0001
Extent Attachment Loss ≥3 mm (Interproximal)	41.8 (19.4)	8.31 (9.03)	<0.0001
Extent Plaque Score ≥1	85.6 (19.4)	70.1 (28.0)	0.001
Extent Gingival Index ≥1	94.5 (10.9)	88.1 (18.6)	0.03
Extent Bleeding On Probing	43.0 (28.2)	31.5 (20.7)	0.03

Table 2

Baseline clinical characteristics of stroke/TIA patients with low and high periodontal disease. Proportions are depicted as (%) and compared using χ^2 test except where indicated.

Clinical Characteristics	HPD (n=40)	LPD (n = 66)	p-value
Age *	61 ± 12	56 ± 16	0.05
Male Gender	68%†	45%	0.03
Non-Caucasian Race	38%	23%	0.10
Hypertension	70%	68%	0.84
Diabetes	25%	15%	0.21
Hypercholesterolemia	75%	64%	0.22
Coronary Artery Disease (CAD)	15%	9%	0.35
Atrial Fibrillation	15%	11%	0.50
Body Mass Index (BMI) *	29.6 ± 7.6	28.6 ± 4.4	0.43
Ever Smoker	58%	53%	0.65
Education **	12 (12,16)	16 (12,16)	0.007
Income **	$33,000 ($18,500,$50,000)	$52,200 ($32,500–$80,000)	0.14
NIHSS ** (Stroke patients only)	5 (3, 7)	3 (2, 5)	0.07
TOAST classification			
Large artery atherothrombosis	13%	8%	0.03†
Cardioembolism	28%	6%	
Small vessel occlusive disease	8%	12%	
Others (Known, Unknown and ≥ 2 causes)	35%	42%	
TIA	18%	32%	0.11
ABCD2 ** (TIA patients only)	4 (4, 5)	3 (3, 4)	0.09

* Normally distributed continuous values are depicted as mean ± standard deviation and compared using t-test

** Continuous variables that are not normally distributed are depicted as median (inter-quartile range) and compared using Mann-Whitney U-test

† **2**×6 contingency table χ^2 test

Table 3

Laboratory characteristics of stroke/TIA patients with low and high periodontal disease.

Clinical Characteristics	High Periodontal Disease (n=40)	Low Periodontal Disease (n = 66)	p-value
Total Cholesterol (mg/dl) *	181 ± 47	185 ± 48	0.74
LDL Cholesterol (mg/dl) *	106 ± 43	107 ± 43	0.90
HDL Cholesterol (mg/dl) *	51 ± 19	52 ± 17	0.66
Triglycerides (mg/dl) **	120 (95,167)	118 (75–165)	0.93
Homocysteine (mcg/dl) **	10.3 (7.3,12.9)	8.3 (6.2,10.7)	0.26
hs-CRP (mg/L) **	3.1 (1.3–5.9)	3.5 (1.1–6.1)	0.68
IL-6 (pg/ml) **	5.0 (2.8–8.4)	2.9 (1.8–4.5)	0.01
s-ICAM (pg/ml) *	377 ± 180	307 ± 123	0.04

* Normally distributed continuous values are summarized as mean ± standard deviation and compared using t-test

** Continuous variables that are not normally dist ributed are summarized as median (inter-quartile range) and compared using Mann-Whitney U-test

Table 4

High periodontal disease: Hazards ratio for recurrent vascular events in stroke/TIA patients.

Unadjusted (Crude)	2.6 (1.2–5.7)
Adjusted (Model 1)*	2.5 (1.1–5.5)
Adjusted (Model 2)**	2.8 (1.2–6.5)
Adjusted (Model 3)***	2.8 (1.2–6.5)

* Adjusted for age and stroke status

** Adjusted for age, gender, education and cardioembolic stroke subtype

*** Adjusted for Age, Gender, Race, Hypertension, Diabetes, Hypercholesterolemia, BMI, coronary artery disease, Smoking, Excessive Alcohol Use, Education level and Annual Income are combined into a single propensity score.

Table 5

Sensitivity Analysis of High Periodontal Disease for unmeasured Binary Confounder (Medication Noncompliance) in Crude Model.

LPD	HPD	Noncompliance HR	HPD HR	95% Confidence interval for High Periodontal Disease HR	
0	0	1.0	2.6	1.2	5.7
10	20	1.1	2.60	1.20	5.69
10	20	1.2	2.60	1.19	5.67
10	20	1.3	2.59	1.19	5.66
10	20	1.4	2.58	1.19	5.64
10	30	1.1	2.49	1.14	5.48
10	30	1.2	2.40	1.09	5.23
10	30	1.3	2.30	1.06	5.05
10	30	1.4	2.23	1.04	4.84
10	40	1.1	2.38	1.09	5.19
10	40	1.2	2.19	1.00	4.77
10	40	1.3	2.02	0.93	4.41
10	40	1.4	1.88	0.86	4.10