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PeRiodontal Treatment to Eliminate Minority Inequality and Rural Disparities in Stroke (PREMIERS): A Multicenter, Randomized, Controlled Study

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Abstract

Background: Stroke remains more common in the "buckle" of the stroke belt, and disproportionately impacts African Americans. The reasons for this racial disparity are poorly understood and are not entirely explained by traditional stroke risk factors. The PeRiodontal treatment to Eliminate Minority InEquality and Rural disparities in Stroke (PREMIERS) study will evaluate the effect of periodontal treatment on recurrent vascular events and stroke risk factors among ischemic stroke and transient ischemic attack patients.

Design: Eligibility for the trial includes a non-disabling stroke confirmed by neuroimaging or Transient Ischemic Attack (TIA), being at least 18 years of age, having ≥ 5 natural teeth with ≥ 2 interproximal sites with ≥ 4 mm of clinical attachment loss and at least 2 sites with probing depth of ≥ 5 mm, and who are able to provide written informed consent. Within 90 days of the index event, patients are randomly assigned to intensive or initial standard cycle of supragingival mechanical scaling, polishing, and oral health instruction and followed for 1 year. The primary outcome is a composite of death, myocardial infarction and stroke or TIA. Secondary outcomes include A1C, fasting lipid profile, triglycerides, high sensitivity C-reactive protein, carotid intimal medial thickness, and blood pressure. A five year enrollment period followed by an addition one year of follow-up is planned.

Summary: The trial will determine whether intensive periodontal treatment reduces the risk of recurrent vascular events among ischemic stroke and TIA patients when compared to initial standard cycle periodontal treatment.

Keywords: Periodontal Disease; Stroke; Stroke Disparities; Adaptive Randomization; Stroke Prevention

Trial Registration: ClinicalTrials.gov NCT 02541032

Background

Stroke is the fifth leading cause of death and the leading cause of long-term adult disability in the United States [1]. Stroke remains more common in North and South Carolina, part of the "buckle" of the stroke belt, and disproportionately impacts African Americans [2]. The reasons for this racial disparity are poorly

understood and are not entirely explained by the traditional stroke risk factors. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study found that tooth loss due to periodontal disease was more common among African Americans than whites and was associated with higher stroke risk and stroke risk factors in the stroke belt [3]. Given this result, REGARDS investigators proposed that periodontal disease may be contributing to the racial disparity in stroke [3]. Additional data from this study shows that low Socioeconomic Status (SES) is associated with greater tooth loss, seen more frequently in African Americans as opposed to their Caucasian counterparts [3]. Considering these factors, a question arises about whether low SES, race, a combination of the two, contribute to tooth loss, periodontal disease, and associated stroke risks. Howard and colleagues suggest in their paper that race is the predominant factor contributing to stroke and other vascular events after adjustment for SES and vascular risk factors [3]. If the predisposition exists among African Americans for greater periodontal disease and vascular events, then what modifications can clinicians recommend to prevent vascular events in this population? This study will examine the racial interaction by enrolling at least 50% of the stroke and TIA survivors from each race, Caucasian and African American. This will allow the team to examine whether there are any SES differences along with any risk factor differences seen between the two races may explain the disparities in stroke and periodontal disease noted in REGARDS. Based on the findings of this study combined with others, there may be new aspects of health that clinicians may need to focus on more to help bridge the inequities found.

The PeRiodontal treatment to Eliminate Minority InEquality and Rural disparities in Stroke (PREMIERS) study was developed to conduct an adequately powered multicenter randomized controlled trial to test whether intensive periodontal treatment reduces the risk of recurrent vascular events among ischemic stroke and TIA survivors in comparison with standard periodontal treatment. Furthermore, this study examines if treatment of periodontal disease attenuates the stroke disparities between Caucasian and African Americans patients found in the REGARDS study [3]. The trial uses the combined resources of established dental centers, Joint Commission Certified Comprehensive Stroke Centers, the Schools of Public Health, and the Institute for Partnerships to Eliminate Health Disparities. The trial addresses specific issues with regard to recruitment of African-American and rural stroke/TIA patients advocating the use of culturally appropriate strategies to educate the study subjects regarding stroke, periodontal disease, and the periodontal-stroke link. Additionally, the trial proposes to study the cost-effectiveness of the periodontal interventions. The main focus is on the financial sustainability of providing aggressive periodontal therapy and standard periodontal therapy (with relatively low expenditures) in exchange for a reduction of recurrent vascular events that may require high cost care provided in the emergency department and inpatient settings. The sustainability of the intervention following the completion of the trial is integrally dependent on the potential cost savings.

Design

Study objective

PREMIERS (www.ClinicalTrials.gov NCT 02541032) is a multicenter, randomized controlled, parallel assignment, double masked, interventional, prevention-focused clinical trial in patients with a recent stroke or TIA who are found to have moderately severe periodontal disease. The primary objective is to evaluate the effect or intensive periodontal treatment on recurrent vascular events and stroke risks factors among stroke and TIA survivors when compared with standard periodontal treatment. Figure 1 illustrates the full study outline in detail. Additionally the study proposes to investigate the cost effectiveness of the proposed periodontal treatment arms. The study is ongoing and approved in each participating site by their respective Internal Review Board.

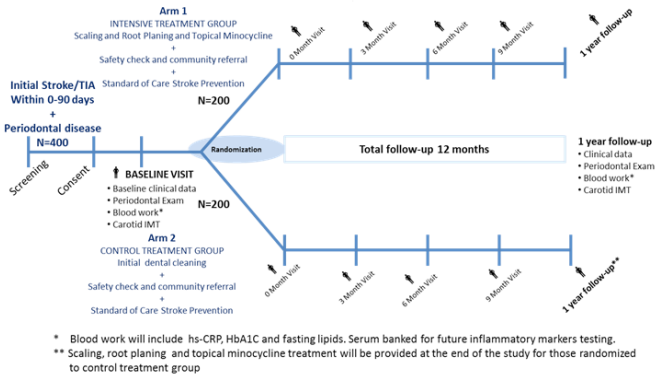

Figure 1: Study Outline.

Study population

Inclusion and exclusion criteria are shown in Table 1. Patients, who have been admitted to the hospital with recent ischemic stroke or TIA (≤ 90 days), are first consented for the screening examinations where they are screened by a calibrated dental examiner for clinical eligibility. An ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral infarction [4]. An eligible ischemic stroke at study entry requires an acute lateralizing or non-lateralizing neurological deficit that is attributable to brain ischemia evident on neuroimaging. If focal, the deficit must persist for at least 24 hours or, if the deficit lasts less than 24 hours, it must be associated with a CT or MR scan

of the brain showing a previously undocumented area of ischemia or infarction located in the expected site of injury. Patients with atherothrombotic strokes, cardioembolic strokes, and strokes caused from small vessel occlusive disease are the focus for eligibility in this study. Therefore, we exclude patients with a stroke related to other causes such as vasculitis, hematological disorders, head trauma, cranio-cervical artery dissection or intra-arterial medical instrumentation that would be likely to cause emboli to the brain (including carotid endarterectomy, percutaneous coronary interventional procedures, coronary artery bypass grafting, intra-aortic balloon pump, valvuloplasty, left-sided electrophysiologic procedures, or cardioversion). If a stroke occurs within 24 hours of a procedure, it is considered related to the medical instrumentation and, therefore, ineligible for enrollment. We also exclude patients with hemorrhagic stroke because of pathophysiological distinction in the mechanism by which periodontal infection may be associated with hemorrhagic stroke [5]. Conversely, focal arterial ischemia with transient symptoms (lasting < 24 hours) and without evidence of infarction by pathology or imaging are considered as a TIA [4]. Eligible symptoms for TIA include hemiplegia or hemiparesis, monoplegia or monoparesis, and a language disturbance other than isolated dysarthria (ABCD score ≥ 4) [2].

Inclusion Criteria
• Patient is at least 18 years of age
• Patient is able to consent, follow an outpatient protocol and is available by telephone
• Non-severely disabling initial stroke (mRS ≤ 3) or TIA in past 90 days
• Evaluable for periodontal examination and treatment (≥ 5 teeth) and able to sustain a dental examination
• Contain ≥ 2 interproximal sites with ≥ 4 mm of Clinical Attachment Loss (CAL)
Exclusion Criteria
• Stroke due to intracranial hemorrhage, dissection, veno-occlusive disease, drugs, trauma, or vasculitis
• Previous neurological impairment that would make detection of a subsequent event difficult
• Co-morbid conditions that may limit survival to less than one year
• Brain CT or MRI that shows a lesion other than stroke as a cause of syndrome
• History of medical conditions requiring antibiotic prophylaxis prior to dental exam
• Patients on Vitamin K anagonist Warfarin with a prothrombin time International Normalization Ratio (INR) less than 2.0 due to increased risk of stroke or greater than 3.5 due to increased risk of bleeding during dental procedures (However, they can still qualify if their Warfarin dose is adjusted and patient's INR is in therapeutic range of 2.0-3.5 in ≤ 90 days for randomization to occur)
• Pregnancy confirmed by urine pregnancy test in women of child-bearing potential (≤ 55 years of age)
• Nursing mothers, due to unknown effect of Arestin® with nursing infants
• Known allergy or hypersensitivity to local anesthesia or minocycline that cannot be medically managed, or bleeding diathesis (genetic or acquired)
• Participation in another randomized clinical trial • Remains within an inpatient rehabilitation center ≥ 90 days after hospitalization

Table 1: Inclusion and Exclusion Criteria.

The periodontal screening examination includes an oral examination including an intraoral soft tissue exam to rule out soft tissue pathology and check for gross carious lesions, broken teeth, grossly faulty restorations, extremely loose teeth, or teeth needing extractions, missing teeth, and to obtain probing depths and attachment levels on all teeth. Radiographs are taken during this screening phase to assess bone loss secondary to chronic infection. The clinical oral examination is performed by a trained and certified dental examiner. Data collection during the periodontal examination includes completing the soft tissue exam, recording Pocket Depths (PD) and Gingival Margin position (GM) using the Carolina Data Acquisition and Reporting Tool (CDART) Dental Toolkit data entry system. These tasks are completed by an examiner with a research coordinator to record data. Patients with at least five natural teeth present and signs of severe periodontitis are considered for enrollment. Any urgent dental treatment that is needed is discussed at this time. Participants are informed of their urgent treatment needs and offered appropriate referrals to

a dentist or community dental clinic. Following the dental exam, the subject is notified of basic study eligibility and steps towards randomization are initiated.

Study procedures

After the patient is consented, information regarding the patient's stroke severity -National Institutes of Health Stroke Scale (NIHSS) obtained at admission, race (questionnaire), SES (questionnaire) and Essen Stroke Risk Score are collected and entered into the CDART data management system [6,7]. Table 2 presents all subsequent timeline assessments for enrolled patients. The patient is subsequently randomized to treatment arms using an adaptive randomization technique referred to as minimization. The minimization method is utilized because this technique has the particular advantage of ensuring treatment groups are similar with respect to several patient characteristics [8]. The characteristics include race, SES, NIHSS and Essen Stroke Risk Score. As each patient is randomized, an imbalance score is calculated across the characteristics based on the prior patients, and the treatment arm that would minimize the imbalance score is selected for the patient with a higher probability, 0.80. If there is no imbalance, the two treatment arms are selected with equal probability.

Timeline	**Screening**	**Baseline**	**3 months ±2 wks.**	**6 months ±2 wks.**	**9 months ±2 wks.**	**12 months ±2 wks.**
Type of Visit	Inpatient	Clinic	Clinic	Clinic	Clinic	Clinic
Clinical Screening/Screener Questionnaire	X					
Dental Screening Informed Consent	X					
Dental Screening	X					
Study Informed Consent		X				
Demographics		X				
SES		X				
Stroke/TIA Information		X				
NIHSS		X				X
ESRS		X				X
Randomization Form		X				
ABCD2		X				
mRS		X				X
Vitals		X				X
Blood Draw/Laboratory		X				X
Medical History		X	X	X	X	X
Behavioral History		X				X
Medications and Medication Compliance		X	X	X	X	X
STOP BANG Questionnaire		X				X
Montreal Cognitive Assessment (MoCA)		X				X
Mediterranean Diet Compliance Questionnaire		X	X	X	X	X
Healthcare Utilization		X	X	X	X	X

Dental Questionnaire		X				X
Periodontal Exam		X	X	X	X	X
Dental CRFs		X	X	X	X	X
Biological Samples (GCF, saliva, plaque)		X		X		X
Carotid IMT Ultrasound		X				X
Periodontal treatment (treatment group specific)		X	X	X	X	X
Stroke Education		X	X	X	X	X
Oral Hygiene Education		X	X	X	X	X
Recurrent Event Follow Up		X	X	X	X	X
Adverse Event (AE)	As Needed					
Serious Adverse Event						
Disposition Form						

Table 2: Timeline of Assessments.

Dental Assessment

Clinical measures of periodontal disease include Plaque Index, Gingival Index, Bleeding On Probing (BOP), probing depth, and Cementoenamel Junction (CEJ) measures relative to the Gingival Margin (GM) on six sites per tooth [9,10]. Clinical Attachment Level (CAL) is calculated from the sum of probing depth and CEJ scores. A three-level case definition of probing depth was independently derived during a meeting by a Centers for Disease Control (CDC)/American Academy of Periodontology (AAP) Working Group on Surveillance Systems for Periodontal Infections and it is as follows: 1) severe periodontitis is diagnosed when there are ≥ 2 interproximal sites (not on the same tooth) with ≥ 6 mm CAL and one or more interproximal sites with probing depth ≥ 5 mm; 2) initial periodontitis is diagnosed when there are ≥ 2 interproximal sites with 4 mm or 5 mm CAL (not on the same tooth) and no interproximal sites with CAL ≥ 6 mm; 3) healthy/no gingivitis results when the individual does not meet the previous criterion [9]. These assessments are conducted at the baseline, 3-month, 6-month, 9-month, and 12-month visit for all enrolled patients.

Periodontal Treatment

The participants are assigned 1:1 to a control treatment group and an intensive treatment group. The control treatment includes supragingival mechanical scaling with an ultrasonic scaler under constant irrigation with filtered water through full mouth prophylaxis to remove only supragingival plaque and calculus. This is followed by supragingival scaling and polishing with abrasive dental polishing paste. The intensive treatment includes initial mechanical supragingival and subgingival debridement and scaling with an ultrasonic scaler and curettes after the administration of local anesthesia, extraction of hopeless teeth, locally (topical) delivered antibiotics, Oral Hygiene Instructions (OHI), and supportive periodontal therapy including periodontal maintenance, local antibiotics and OHI at each subsequent study visit [9,11-13]. Periodontal scaling and root planning is performed with a Cavitron Ultrasonic scaler for Gross Debridement and periodontal curettes for more refined instrumentation. The intensive group completes up to five sessions of full-mouth intensive removal of dental plaque biofilms. Extraction of hopeless teeth follows subgingival scaling and root planning in the intensive arm or at the final visit for those assigned to the control arm. Hopeless teeth, class III furcation and/or grade ≥ 3 mobility and/or periodontal lesions approaching within 3 mm of the apices, are extracted as part of the therapy. Minocycline is locally administered to those participants within the intensive arm at every visit and those in the control arm at their final visit. The local administration allows for the antibiotic to be placed without crossing into the bloodstream and producing systemic effects [14,15]. An instruction on oral hygiene is provided to participants enrolled into both arms. Supportive periodontal therapy is provided to those randomized into the intensive arm and consists of supragingival mechanical scaling and prophylaxis as indicated and, the application of minocycline microspheres into the remaining periodontal pockets ≥ 5 mm.

Patients in the intensive-treatment group undergo up to five appointments within a period of one month to bring the oral infection and inflammation under control and are provided with a

state-of-the-art ultrasonic toothbrush (Sonicare Flexcare Platinum Sonic Toothbrush) as well as an interdental cleaner (Sonicare Airfloss Plus) loaded with Sonicare BreathRx Antibacterial mouth rinse [16]. Local anesthesia is used as needed in accordance with current clinical guidelines. Any hopeless teeth are extracted during this treatment period. In addition to standard scaling and root planing, we seek to better suppress the oral biofilm by administering minocycline locally. These microspheres of minocycline (Arestin®, OraPharma) are delivered locally into the periodontal pockets ≥ 5 mm. The goal of this intensive treatment is to keep bleeding scores < 20%. These patients are re-examined at 3, 6, 9 and 12 months and receive supportive maintenance care consisting of supra- and sub-gingival scaling and prophylaxis as needed. Any sites with bleeding on probing with probing depths ≥ 5mm will receive Arestin® again. New Sonicare Adaptive Clean Standard sonic toothbrush heads, Airfloss Pro nozzles and BreathRx mouth rinse is provided every three months. Thus, during the treatment period bleeding on probing scores and probing measurements is monitored to measure the efficacy of the treatment.

Patients in the control/minimal-treatment group receive full-mouth supragingival mechanical scaling and polishing at baseline. They are informed of the presence and severity of their periodontal disease and advised to be seen by their dentist if their oral condition requires immediate attention. If they have no dental provider they are referred for care. All patients, including the control/minimal treatment group are reexamined at 3, 6, 9 and 12 months to assure safety. Among the control/minimal treatment group, the periodontal condition is monitored to assure there is no progression of disease. If any site demonstrates an increase in pocket depth > 3 mm, they receive site-directed scaling and root planing and then they are followed in the study until the end (12-months). At the final 12-month visit they are provided option of intensive treatment listed above.

All periodontal assessments as well as treatment (both groups) are conducted by periodontists, dentists or dental hygienists who are licensed, trained, and calibrated. This protocol specific training and calibration includes not only standardization of clinical measurement, but treatment procedures as well. To maintain examiner blinding throughout the study, the treatment provider is a person other than the dental examiner and exclusively provides treatment and does not participate in patient assessments. Thus, one person conducts the measurements on the patient and then patient moves to different examiner for the treatment to take place. This allows for the examiners to be masked from one another. Clinical dental measures include UNC Modified Plaque Index, Modified Gingival Index, Bleeding On Probing (BOP), probing depth and Cementoenamel Junction measures relative to the gingival margin (CEJ) on six sites for all teeth using the UNC 15 probe [17,18]. Clinical Attachment Level (CAL) is calculated from the sum of probing depth and CEJ scores. At the completion of the study, the control/minimal treatment patients are offered the same dental care provided to the intensive treatment group as needed.

Trial outcomes

The study will use major adverse cardiovascular events in the form of ischemic stroke/TIA, MI, and cardiovascular death as the primary outcome events. All primary and secondary outcomes are denoted in Table 3. Outcome events are adjudicated by the site Principal Investigator and analyzed as composite of all outcomes. Ischemic stroke is diagnosed when a patient develops a new focal neurological deficit that is sudden in onset, thought to have a vascular cause, lasts at least 24 hours, and is not associated with a brain hemorrhage on brain CT or MRI when available. Situations where symptoms last < 24 hours without evidence of a new infarct is regarded as TIAs if they meet the criterion for TIA diagnosis. Acute MI is defined according to criteria modified from the 2000 Consensus Conference of the European and American Colleges of Cardiology, based on symptoms and electrocardiogram changes, in conjunction with contemporary biochemical markers of myocardial necrosis (troponin or creatine kinase) [19]. Cardiovascular Death is classified as 'cardiac death' or 'other cardiovascular death'. Cardiac death must have a cardiac cause as the main reason for death. All other cardiovascular deaths are defined as 'other cardiovascular death' (e.g. stroke, bleeding episode, pulmonary embolism, and procedural). Etiological classification of stroke is classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [7]. This analysis, along with stroke sub-typing, will help differentiate between cardioembolic versus atherothrombotic events arising from shared risk factors.

Primary Outcomes
Stroke (ischemic, intracerebral hemorrhage, subarachnoid hemorrhage, or hemorrhage of uncertain type)
Myocardial Infarction (MI) (fatal and non-fatal)
Transient Ischemic Attack (TIA)
Death
Secondary Outcomes
A1C
Total Cholesterol
HDL
Triglycerides
LDL
hsCRP
Carotid IMT
Blood Pressure

Table 3: Trial Outcomes.

There are several secondary outcomes that will be analyzed including carotid artery Intimal Medial Thickening (IMT), high sensitivity C-Reactive Protein (hs-CRP), blood pressure, hemoglobin A1C, and fasting lipid profile [18-20]. The carotid artery IMT will be used to measure the progression of atherosclerosis during the study period which has been shown to be a risk factor for myocardial infarction and stroke [20,21]. The carotid IMT will be measured by B-mode ultrasound and analysis will be based on the mean IMT of the far wall for 1-cm lengths of the right and left carotid bifurcation and internal and common carotid arteries. Blood pressure will be recorded as an averaged triplicate reading from a semiautomatic Omron oscillometric BP monitor. Serial blood samples will be collected and assessed for hs-CRP, hemoglobin A1C, and fasting lipid profile in a blinded fashion to assess stroke risk [22]. All secondary outcomes are collected at both the baseline and 12-month final visit for each enrolled participant. Motivational Interviewing (MI) is also utilized to encourage behavior change based on issues that the patient self-identifies throughout the study in an effort to further reduce their risk of recurrent stroke, enhance their mood post stroke, and improve their post-stroke mortality [23,24]. The MI is conducted at each study visit beginning at baseline and finishing at the 12-month final visit for those participants who agreed to participate within this portion of the trial. Additionally, we are also conducting an economic evaluation of the periodontal intervention from the budgetary perspective. The main focus will be on the financial sustainability of providing aggressive periodontal therapy in exchange for a reduction of uncertain recurrent vascular events that may require high cost emergency department utilization and/or inpatient care.

Statistical considerations

Our sample size estimation was based on preliminary data collected using longitudinal data in a cohort of 106 stroke/TIA patients with a high 12-month composite event rate of 14% [25]. We estimate that the 12-month event rate in the intensive treatment arm will mimic that seen in stroke/TIA with minimal to mild PD (12%) and that in the control/minimal treatment arm will mimic that in moderate to severe PD (30%) translating to an odds ratio of 0.32. In the investigation of treatment effects, we will model whether a participant had one or more recurrent vascular event(s) (primary outcome) using logistic regression and we will model the number of recurrent vascular events using Poisson regression. Accordingly, the required sample size to detect a medium effect is approximately 64 per group; this translates to having power to detect an odds ratio of at least 0.26 in logistic regression or an incidence rate ratio of 0.39 in Poisson regression.

Given our plan to enroll 140 evaluable patients per group, we will have 80% power to detect an odds ratio of 0.445 for treatment (and 0.298 for the race by treatment interaction) 10% attrition, or to detect an odds ratio of 0.467 for treatment (and 0.324 for the race by treatment interaction) 0% attrition. Similarly, we will have 80% power to detect an incidence rate ratio of at least 0.371 for treatment (and 0.215 for the race by treatment interaction) if there is 10% attrition, or to detect an incidence rate ratio of 0.394 for treatment (and 0.242 for the race by treatment interaction) if there is no attrition. Since we anticipate very little attrition (~10% missing data), the trial is powered to detect effect sizes that are between small and medium standardized sizes (approximately at 0.30 standard deviations). To power the study to detect small effect sizes (0.20 standard deviations) would require 393 participants per group, which would exceed the size of the pool from which we can recruit.

Although the effect of PD on secondary outcomes has been studied in patients with cardiovascular disease, it has not been investigated in stroke/TIA [26,27]. Power for secondary outcomes that are binary or count in nature are governed by the above calculations. In addition to such outcomes, we will also investigate secondary outcomes (e.g., lipids) that are continuous via linear regression models. In such models, with a total sample size = 140, alpha = 0.050, overall probability of positive outcome = 0.450, R2 of (A) or (B) with all covariates = 0.400 [(A) Percent of binary covariate equal to 1 (treatment) = 50.0%, (B) Percent of binary covariate equal to 1 (race-by-treatment) = 25.0%]. We will have an 80% power in logistic regression to declare as significant parameter associated with an estimated odds ratio of (A) 0.445 and (B) 0.371. Thus, the power of the study to detect race-by-treatment interaction is over powered and will address issues such as attrition.

In addition to the analyses described above, we will also collect the times at which periodontal treatments were applied as well as the times at which recurrent vascular events occurred. These additional data will then permit Cox proportional hazards models to estimate hazard ratios. Power to detect significantly lower hazard is similar to the power calculations already presented. Data are summarized using Kaplan-Meier curves and initial differences assessed using log rank tests. Poisson regression models are compared to negative binomial models and to zero-inflated versions of these count models. Covariates that have significant main effects in the multivariable logistic regression models or confounded the association between treatment arm and outcome by at least 10% are retained in final models. Bivariate relationships between exposure and time to event (clinical outcome) are assessed by Kaplan-Meier survival analysis using the log-rank test, followed by estimation of a multivariable Cox Proportional Hazard regression model.

Discussion

The PREMIERS clinical trail is one of the first trails to date to test the effect of treating periodontal disease on major cardiovascular adverse events in recent stroke/TIA patients. The PREMIERS clinical trial differs in unique ways from other stroke prevention trials. First, it fosters collaboration between the vascular, neurological and dental fields together in the treatment of recent stroke/TIA patients. This unique approach allows the participants to have experts in both fields oversee their care and treatment in prevention of recurrent events throughout the duration of the study. The Neurologist is seen first at each visit to ensure all stroke-related risk factors are controlled and their vital signs are within acceptable limits to receive dental care. Information regarding physician visits, hospitalizations, and stroke preventive medication (antiplatelet, statins, anti-hypertensive and antidiabetic medications) changes since the last study visit are obtained and discussed at this time. The dental hygienist evaluates the patient next to collect all reportable measures for the study including plaque and gingival indices. Lastly, the dentist evaluates the patient with a soft tissue exam and recommends any treatment at that time.

Second, PREMIERS was established with a disparity focus in mind, since the reasons for racial disparities in stroke are poorly understood [3]. The patients seen within the healthcare facilities of this study are racially distributed with approximately 50% Caucasians and 50% African Americans, making this a well-suited population of patients to study. In order to address the disparities within the population of patients, motivational interviewing is utilized to assist the participants with identifying personal goals they can work on that will further reduce their stroke risk. Personal goals could include any of the following: dietary changes, physical activity, weight loss, smoking cessation, etc. The incorporation of motivational interviewing within the study will result in enhanced knowledge around stroke disparities.

Third, the study utilizes an adaptive randomization technique called minimization, which takes into account different scores such as NIHSS, demographic characteristics, SES and stroke risk factors when assigning the patient to the treatment arms. The minimization method ensures that treatment groups are similar based on the characteristics mentioned previously [28]. This method offers an alternative to stratified randomization that has been noted to be a superior technique [29,30]. Trials that use minimization are considered methodologically equivalent to randomized trials according to the Consort Statement [30]. When utilizing this method, a randomization list is not set up in advance; rather the first patient is randomized to one of the treatment groups with equal probability. Subsequently, each patient is randomized with 80% probability to the treatment group that would minimize the imbalance between groups with respect to stroke severity, race, SES, and stroke risk score making this a distinctive trial.

Lastly, PREMIERS was developed so that the control group has a staggered intensive periodontal treatment plan, resulting in having their gum disease treated within the first year of their stroke/TIA. While the safety of intensive periodontal treatment after an ischemic stroke or TIA are not known, the patients with moderate to severe periodontal disease may benefit from intensive periodontal treatment. Links between periodontal disease and risk of stroke/TIA are well established and our study population may gain particular benefit from intensive treatment of periodontal disease [25,31-33], delayed to the end of the first year from the index event in the control arm.

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Disclosures

No potential conflict of interest reported by the authors.

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