DR. ANDREA RAVIDÀ (Orcid ID : 0000-0002-3029-8130)

DR. GIUSEPPE TROIANO (Orcid ID : 0000-0001-5647-4414)

DR. HSUN-LIANG CHAN (Orcid ID : 0000-0001-5952-0447)

PROF. HOM-LAY WANG (Orcid ID : 0000-0003-4238-1799)

Article type : Original Article Clinical Periodontology

Maintenance visit regularity has a different impact on periodontitis-related tooth loss depending on patient staging and grading

Andrea Ravidà[1]*, Matthew Galli[1]*, Muhammad Saleh[1,2], Maria Vera Rodriguez[1], Musa Qazi[1], Giuseppe Troiano[3], Hsun-Liang Chan[1], Hom-Lay Wang[1]

[1]Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, MI, USA

[2]Department of Periodontics, University of Louisville School of Dentistry, Louisville, KY, USA.

[3]Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy.

*These authors contributed equally to this paper

Correspondence to:

Hom-Lay Wang, DDS, MSD, PhD

Department of Periodontics and Oral Medicine

University of Michigan School of Dentistry

1011 North University Avenue

Ann Arbor, Michigan 48109-1078, USA

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/JCPE.13489

This article is protected by copyright. All rights reserved

Author Manuscript

TEL: +1 (734) 763-3325
E-mail address: homlay@umich.edu
ORCID: 0000-0003-4238-1799

Author Manuscript

Running title: Impact of maintenance regularity on periodontal tooth loss
Word count: 4,347 words
Tables and figures: 4 figures, 3 tables, 7 supplementary tables
Number of references: 27
Key words: periodontitis, supportive periodontal maintenance therapy, tooth loss, staging and grading.

Conflict of interest: The authors do not have any financial interests, either directly or indirectly, in the products or information listed in the paper.

Data Availability Statement: Data available on request from the authors

Clinical Relevance

Scientific Rationale: The 2017 World Workshop introduced a multidimensional classification system for periodontal diseases. A deep analysis of maintenance quantity, regularity, patterns, and the consequences of missing visits based on periodontal staging and grading is needed.
Principal Findings: Maintenance visit regularity and missing multiple years of maintenance have a larger impact on risk of periodontal tooth loss in patients with higher staging and grading. The recommended maintenance frequency is 6 months and should be increased for at-risk populations (former and current smokers, diabetics, and elderly patients).
Practical Implications: Patient stratification based on staging and grading can serve as the foundation for personalized supportive periodontal care.

Abstract

Aim: To assess if maintenance variables have a differential effect on tooth loss due to periodontitis (TLP) based on staging and grading.

This article is protected by copyright. All rights reserved

Materials and Methods: Patients treated for periodontitis for a minimum of ≥10 years follow-up were included and categorized according to their stage and grade at baseline. Impact of number, regularity, and pattern of supportive periodontal therapy visits (SPT) on TLP was explored by dividing teeth into test (5-year time periods prior to TLP events) and control groups (random 5-year periods without tooth loss).

Results: The regularity of maintenance visits, but not the overall quantity, had a significant impact on risk of TLP and showed higher importance as staging and grading increased (larger impact for stages III/IV and grade C). The minimum threshold of visits below which the risk of TLP was equivalent to that of the control group was one visit every 7.4 months for stages I-II, 6.7 months for stage III-IV, 7.2 months for grade B, and 6.7 months for grade C. This frequency should be increased for former and current smokers, diabetics, and elderly patients. Stage III and IV patients who skip more than one year of maintenance in a 5-year period have an increased risk of TLP (OR=2.55) compared to those only miss one year. A similar trend was noted for grade C patients, but not for stages I/II or grades A/B.

Conclusions: Lack of SPT regularity and missing multiple years of maintenance had a larger influence on risk of TLP for higher-level staging and grading.

Author Manuscript

Introduction

Periodontitis is likely the most prevalent chronic inflammatory disorder worldwide (Chapple, 2014) and its pathogenesis is characterized by a biologically destructive interaction between the host immune system and subgingival microflora. Treatment of this complex disease, especially in advanced cases, requires a lifelong commitment to regular maintenance therapy in conjunction with high-quality oral hygiene long after the completion of corrective therapy. In other words, treatment does not end with active periodontal therapy (APT), but actually starts with it.

It is thus simple to understand the results of studies indicating that APT without supportive periodontal therapy (SPT) is of little value in restoring and maintaining periodontal health (Becker, Berg, & Becker, 1984; Chambrone, Chambrone, Lima, & Chambrone, 2010; Eickholz, Kaltschmitt, Berbig, Reitmeir, & Pretzl, 2008; Graetz et al., 2017; Pretzl, El Sayed, Weber, Eickholz, & Baumer, 2018). In fact, the damaging effects of poor attitudes towards oral health are bidirectional, causing a deterioration of both

This article is protected by copyright. All rights reserved

compliance with professional care and self-directed oral hygiene over the course of time (Ojima et al., 2005). Poor compliance with SPT paves the way for recurrent periodontitis and subsequent tooth loss (McFall, 1982). By the same token, several studies have shown that compliance with SPT recommendations allows periodontal patients to retain many of their teeth (Becker et al., 1984; Cortellini, Buti, Pini Prato, & Tonetti, 2017; McFall, 1982; Ramfjord et al., 1982).

A uniform approach towards SPT will rarely meet the individual needs of each patient and may potentially result in either under- or over-provision of treatment. SPT should not be viewed from a "one size fits all" standpoint and serves as a prime opportunity to stratify patients based on disease risk in order to deliver personalized care (Kornman & Duff, 2012; Lang & Tonetti, 2003; Meyer-Baumer et al., 2012). SPT should ideally be tailored to each case based on response to treatment, severity of baseline disease, oral hygiene status, and presence of established periodontal risk factors including uncontrolled diabetes and smoking (Lang, Suvan, & Tonetti, 2015; Lang & Tonetti, 2003; Matuliene et al., 2010; Trombelli, Simonelli, Franceschetti, Maietti, & Farina, 2020). The concepts of risk assessment and personalized treatment were implemented in the 2017 classification of periodontitis (Tonetti, Greenwell, & Kornman, 2018). Although the recent classification system is conceptually based on traditional TNM staging and grading systems which have long been utilized in cancer diagnosis and treatment, it also provides the necessary framework for inclusion of biomarker-based diagnostics for enhanced prognostication, disease detection, and risk stratification (Tonetti et al., 2018). The literature has not yet explored the potential connection between the recently introduced staging and grading classification system, SPT frequency and regularity, and tooth loss due to periodontitis (TLP).

A sophisticated analysis of compliance should ideally take into account maintenance quantity, frequency, regularity, and patterns (ie. uphill and downhill trends in SPT frequency) (Ramseier et al., 2019), as well as the impact of 'gap years' (years with zero maintenance visits) (Eickholz et al., 2008; Pretzl et al., 2018). In addition, the extent of variability of SPT visits in relation to the mean (coefficient of variation). Hence, the aim of the current study was to retrospectively assess the interrelationship between periodontitis staging and grading at the t of APT, the aforementioned SPT variables, and TLP during the follow-up. Our hypothesis was that maintenance variables would have differential effects on TLP based on periodontitis staging and grading throughout a long-term follow-up.

This article is protected by copyright. All rights reserved

Author Manuscript

Materials and Methods

The present retrospective study was conducted in accordance with the Helsinki Declaration of 1975 (World Medical Association, 1975) as revised in 2013 (World Medical, 2013). The protocol was approved by the University of Michigan, School of Dentistry, Institutional Review Board for Human Studies (HUM00157260).

Study population and data extraction

Data was obtained from the physical and electronic charts of patients who received nonsurgical and, if indicated, surgical corrective therapy between January 1966 and January 2008 at the University of Michigan School of Dentistry, Ann Arbor, MI, USA. Eligibility criteria, data collection, and classification of patients at baseline using 2017 World Workshop case definitions including stage (I, II, III, and IV), grade (A, B, and C), and extent (localized, generalized, and molar-incisor pattern) (Tonetti et al., 2018) are described elsewhere (Ravida et al., 2020).

Briefly, patients treated for periodontitis with a session of scaling and root planing (SRP) and/or surgical therapy that had a complete medical history, baseline periodontal charting, full-mouth radiographs, and a minimum of ≥10 years follow-up at the University of Michigan School of Dentistry were included. Patients that underwent care and maintenance outside the School of Dentistry during the follow-up period were excluded. The follow-up period ran from baseline (T0: the first SPT appointment at the periodontal department) up to the date of the last SPT visit with available data (T1). Relevant patient information such as the exact number of SPT visits per year after baseline, and relevant medical history (history of diabetic status and self-reported smoking history at baseline) was collected. Radiographic bone loss (% of root length) at baseline was measured from periapical radiographs to assess periodontitis stage and grade (Pepelassi, Tsiklakis, & Diamanti-Kipioti, 2000). Tooth-specific clinical data including probing depth, clinical attachment level, bleeding on probing, and furcation involvement were obtained. Information about masticatory dysfunction, drifting, flaring, bite collapse, and biofilm accumulation were retrieved from patient records where available. Staging and grading algorithms published by Tonetti et al. (Tonetti et al., 2018) were utilized to categorize patients using baseline clinical and radiographic parameters. Extent was evaluated after classifying stage and was calculated as the percentage of teeth at

This article is protected by copyright. All rights reserved

Author Manuscript

the stage-defining severity (Sanz, Papapanou, Tonetti, Greenwell, & Kornman, 2020b). Baseline staging and grading was conducted by a single investigator (MS) after being calibrated by one of the authors of the new classification system (Henry Greenwell) and was based on clinical and radiographic records at T0 (Tonetti et al., 2018).

Patient charts were reviewed for TLP by evaluating the number of teeth present at T0 up to T1. For each non-third molar that was lost, the date and reason for extraction were analyzed. The reasons for extractions were always recorded in the patient files as per clinic policy. Teeth extracted due to periodontitis during the active treatment phase (at or prior to T0) were not considered in analyses of TLP but were instead used to evaluate the baseline stage of patients as recently suggested by Sanz and coworkers (Sanz, Papapanou, Tonetti, Greenwell, & Kornman, 2020a). In cases where teeth were extracted due to concomitant pathologies (i.e., some combination of periodontitis, caries, fracture, or periapical pathology), the overriding reason for tooth loss was evaluated by the specialist who deemed the tooth hopeless. Additionally, for the rare cases where the reason for tooth loss could not be accurately ascertained (21 teeth in total), the tooth loss event was not considered as TLP. At the re-evaluation after active therapy, the deepest probing pocket depth (PPD) was collected and the teeth were divided into three groups based on the site with the deepest probing depth (≤4mm, 5mm, or ≥6 mm). Presence of bleeding on probing (BOP) was assessed in a binary manner (yes/no).

Study aims and data processing

The primary aim of the study was to explore the influence of the interrelationship between maintenance variables and baseline stage and grade on TLP throughout a long-term follow-up. Specifically, the present study aimed to assess if the number, regularity, and pattern of maintenance visits played a larger role in risk of TLP in patients with more severe forms of periodontitis (stages III/IV) compared to less severe forms (stages I/II), as well as in patients with faster rates of disease progression (grade C) compared with slower (A/B). In addition, the present study aimed to assess the impact of missing one or more years of periodontal maintenance ("gap years") on the occurrence of TLP. A secondary aim included calculating a threshold value for maintenance frequency based on patient staging and grading below which the risk of TLP was minimized.

From a patient standpoint, tooth loss may end up increasing compliance. Patients losing teeth may end up being more motivated to attend their scheduled SPT visits. One tactic to address this potential inverse relationship (or confounding by indication) is to employ a

This article is protected by copyright. All rights reserved

Author Manuscript

statistical technique based on time-dependent covariates where tooth loss is related to past noncompliance, not future noncompliance which may skew the results (Hujoel, Leroux, Selipsky, & White, 2000).

To allow for a precise analysis of the influence of maintenance regularity on TLP events, teeth were assigned to test (tooth was lost due to periodontitis during the follow-up) or control (tooth was not lost) groups. For test teeth, 5-years periods prior to TLP were analyzed. For control teeth, random 5-years periods not associated with tooth loss (for any reason) were analyzed. Control periods included in the analysis were separated by a duration of 5 years before or after any TLP event experienced by that patient during the follow-up. Each tooth contributed a maximum of one time period, and 5-year periods starting before the first follow-up were excluded. If a patient presented with more than 1 TLP event (>1 test teeth), all of the events were analyzed. If a patient had zero TLP events during the follow-up, only one random 5-year control period was selected. Figure 1 illustrates the data pre-processing algorithm, conducted as described above.

Different variables related to maintenance were evaluated to compare the pre-TLP and control 5-year periods for each stage and grade subgroup:

- Total number of maintenance visits (NMV): Example: 1 3 0 1 1, NMV=6
- Coefficient of variation (CV = SD x 100/mean) of the total number of maintenance sessions: Example 1: 1 2 1 2 1, CV=39.1%; Example 2: 5 5 5 5 5, CV=0.0%; Example 3: 0 5 0 5 0, CV=136.9%
- Patterns in the number of maintenance visits:
    - Uphill: increase in annual number of visits: Example: 1 2 2 2 2; 0 1 1 1 2
    - Stable: consistent number of annual visits: Example:1 1 1 1 1
    - Downhill: decrease in annual number of visits: Example: 3 1 1 0 0 ;1 0 0 0 0
    - Irregular/no pattern: no discernable pattern: Example: 1 2 0 3 1

It should be noted that the coefficient of variation was introduced for the first time in the periodontal literature in the present article. Recommendations for maintenance frequency according to baseline stage and grade were based on multivariate modelling and descriptive statistics. In addition, a separate analysis was done to investigate the impact of non-compliance based on a minimum of one visit/year speculated in several studies to be the cut-off frequency beyond which more significant tooth loss occurs (Farooqi, Wehler, Gibson, Jurasic, & Jones, 2015; Rosen et al., 1999). To perform this analysis, patients were divided into three groups based on the number of gaps during the 5-year periods:

- No gaps group: Patients visiting at least once per year: 1 1 2 1 2; 1 1 1 1 1; 3 1 2 2 2

This article is protected by copyright. All rights reserved

Author Manuscript

- One gap group: Patients who had one annual absence: 0 1 2 1 3; 1 1 1 0 1
- Multiple gaps group: Patients who had more than one annual absence: 1 1 2 0 0; 1 0 1 0 2; 0 1 0 2 0

Statistical analysis

At the tooth-level and for each stage and grade, the outcomes by TLP or type of period (pre-TLP/control) were related to the maintenance parameters of the 5-year periods using multi-level logistic regression with generalized estimation equations (GEE) to take into account the dependence of observations (multiple teeth from each patient). The GEE models were developed at the tooth-level, considering the dependence of intra-patient data. Some of the predictor variables included were patient-level evaluations (age, maintenance characteristics, periodontal disease classification); but PPD and bleeding on probing (BoP) were measured at the tooth level and it is optimal to keep them in the GEE model, since the outcome (TLP) is also a tooth level parameter. Bivariate analysis was conducted for each parameter adjusted by patient age at the beginning of the 5-year period. A multivariate model was also constructed including significant ($p<0.05$) or marginally significant parameters ($p<0.1$). Odd ratios and 95% confidence intervals were obtained from the Wald´s Chi^2 statistic. The significance level used in analyses was 5% ($\alpha=0.05$).

Regarding the power analysis, a post-hoc estimation was obtained. A sample size of 11,125 independent teeth provided 99.9% power at 95% confidence for detection of a relative risk (RR) of 3.0 as significant using a Cox multiple regression model to assess the influence of a two-level factor (e.g. stage), assuming that 95% of observations were censored. However, teeth cannot be considered independently, and the power calculation was corrected because of the two-level structure of data. Each patient provided 25 teeth on average and within-subject correlation CCI=0.5 (moderate) was assumed, leading to a correcting coefficient D=13.0. Therefore, 11,125 dependent teeth provided the same power as 855 independent teeth, calculated at 88% power under the same conditions (RR=3.0; 95% confidence).

Results

Characteristics of patient cohort

The overall sample included 11,125 teeth (mean number of 25.2 ± 3.2 teeth per patient at T0) in 442 patients treated for periodontal disease. In total, 219 males (49.5%) and 223 females (50.5%) with a mean age of 47.5 ± 11.8 years at baseline (range: 17 to 76 years) were included. Patients were followed for a mean period of 272.5 ± 80.7 months (22.7 ± 6.7

This article is protected by copyright. All rights reserved

Author Manuscript

years) over a range of 121 to 580 months (10.1 to 48.3 years). Overall, 45 patients were classified as stage I (20 grade A and 25 grade B), 134 were stage II (11 grade A, 104 grade B, and 19 grade C), 214 were stage III (8 grade A, 134 grade B, and 72 as grade C), and 49 were stage IV (3 grade A, 23 grade B, and 23 grade C). In total, 554 teeth (4.98%) were extracted in 205 patients due to periodontitis during the follow-up. Of these, 184 (1.65%), 223 (2.04%), and 147 (1.37%) were lost from 0-10 years, 10-20 years, and >20 years follow-up, respectively.

Comparison between pre-TLP and control time periods based on NMV, CV, pattern, age, and periodontal diagnosis

Overall comparison

Results of logistic regression by GEE analysis are shown in Table 1. Stage III and IV, grade C, age, and CV were significantly associated with TLP ($p<0.05$). Specifically, one additional percentage in CV during the 5-year period corresponded to a 1% increase in TLP risk ($p=0.001$). NMV did not significantly influence risk for TLP.

No association between patterns of maintenance visits (ie. uphill, downhill) and TLP during the pre-TLP and control time periods were found for stages II-IV (Suppl. Table 1) or any of the grades (Suppl. Table 2). Patterns of maintenance visits could not be analyzed for stage I or grade A patients due to the low amount of TLP events in these subsets.

Comparison between pre-TLP and control time periods for stage I-II patients

When just stage I and II patients were analyzed, NMV and CV were not associated with risk for TLP (Table 2). Only grade C ($p<0.01$) disease discriminated significantly between pre-TLP and non-TLP periods in the statistical model.

Comparison between pre-TLP and control time periods for stage III-IV patients

When only patients with stage III and IV disease were included in the analysis, CV, age, PPD after active therapy and grade C showed a significant effect on risk for TLP ($p<0.05$) (Table 2). NMV and BOP were not associated with risk for TLP ($p>0.05$).

Comparison between pre-TLP and control time periods for grade A patients

GEE analysis was not performed due to the small sample size and the limited number of TLP in this subgroup.

This article is protected by copyright. All rights reserved

Author Manuscript

Comparison between pre-TLP and control time periods for grade B patients

Age, stage III, stage IV and PPD after active therapy discriminated significantly between pre-TLP and control periods ($p<0.001$) (Table 3). NMV and CV did not exhibit a significant effect on risk for TLP for grade B patients. When GEE model was adjusted by patient age as well as smoking and diabetic status (Suppl. Table 3), age ($p<0.001$) and smoking status ($p=0.039$) both exhibited a significant impact on risk for TLP.

Comparison between pre-TLP and control time periods for grade C patients

Diagnosis with stage IV disease and PPD after active therapy discriminated significantly between pre-TLP and control periods ($p<0.042$) (Table 3). A strong trend was noted for CV ($p=0.092$). When the model was adjusted by patient age, smoking, and diabetic status (Suppl. Table 4), CV exhibited a significant influence on risk for TLP ($p=0.016$). Additionally, a positive diagnosis for diabetes at baseline was associated with a 4.69-fold greater risk for TLP compared to patients with a normoglycemic status ($p=0.004$).

Minimum recommended number of periodontal maintenance visits

Descriptive analysis demonstrated that both NMV and CV were similar between pre-TLP and control periods for stages I-II (Figure 2A). However, for stages III-IV as well as for grades B and C, NMV was lower and CV was higher in the 5-year pre-TLP periods relative to control periods (Figure 2B, C, D). Grade A could not be evaluated due to the limited number of pre-TLP periods available in the dataset (16 periods). Complete analyses leading to assessment of the threshold minimum number of recommended maintenance visits as well as the possible combinations of annual visits that were associated with a decreased risk of TLP are explained in detail in Supplementary Table 5. The minimum threshold of visits below which the risk of TLP was equivalent to that of the control groups was one visit every 7.4 months for stages I-II, every 6.7 months for stage III-IV, 7.2 months for grade B, and 6.7 months for grade C. The recommended frequency of maintenance visits should be increased for diabetic patients, former/current smokers, and older patients.

Impact of missing one or more years of SPT on risk for TLP in 5-year periods

No gaps vs. one gap

Results of logistic regression by GEE modelling in the entire population controlling for NMV, CV, and compliance (no gaps vs. 1 gap) demonstrated that the presence of one gap during the 5-year periods did not significantly influence the risk of TLP (Suppl. Table 6A).

This article is protected by copyright. All rights reserved

Author Manuscript

However, CV, age, stage III, stage IV, and grade C showed a significant effect. Sub-analyses based on stage (stages I-II and III-IV) or grade (grades A-B and C) showed similar results regarding the influence of up to one gap year (Suppl. Table 6B-E). CV had a significant effect for stages III-IV (p=0.005) and grade C (p=0.046), while age displayed significance for stages III-IV and grades A-B.

One gap vs. multiple gaps

Results of logistic regression by GEE modelling controlling for NMV, CV, and compliance (one gap vs. multiple gaps) demonstrated that the presence of multiple gaps during the 5-year periods did not significantly influence the risk of TLP in the overall population (Suppl. Table 7A). However, age, stage III, stage IV, and grade C showed a significant effect. Sub-analyses demonstrated that missing multiple years of maintenance was not a significant variable for stages I-II (p=0.5) (Suppl. Table 7B), but reached significance for stages III-IV (p=0.003) (Suppl. Table 7C). No difference was found for grades A-B (p=0,33) (Suppl. Table 7D). For grade C patients, a trend was noted where multiple gap years increased the risk of TLP (OR=2.31; p=0.070) compared to one gap in a 5-year period (Suppl. Table 7E). NMV and CV both did not show any significant effects in any of the models.

Impact of multiple gaps and age on probability of TLP

Results from GEE modelling were used to construct graphs illustrating the probability of TLP based on the number of gaps (0-5) within included 5-year periods and patient age (Figure 3). As the number of gap years increased within a 5-year period, so did the probability of TLP. Additionally, as age increased, the probability of TLP also increased. Higher staging and grading were associated with a higher risk of TLP as denoted by comparing the slopes of the curves between stages I-II vs. III-IV, and grades A-B vs. C. Finally, at higher staging and grading, the consequences of gap years on probability of TLP increased as noted by a wider spread between the curves.

Discussion

Supportive periodontal therapy: current evidence and grey zones

The recent periodontal classification system provides a multidimensional framework for stratifying patients based on stage (complexity of case management and disease severity)

This article is protected by copyright. All rights reserved

Author Manuscript

and grade (rate of progression and risk factors) with the ultimate goal of encouraging a precision medicine-centric philosophy towards patient care (Papapanou et al., 2018). SPT serves as an important checkpoint during the course of treatment to monitor disease status, evaluate the response to corrective treatment, and provide patient education. Ideally, SPT should be tailored both in terms of recommended interval and therapeutic approach and modified based on patient-specific variables (Trombelli et al., 2020). However, the literature has never before validated how risk stratification according to staging and grading may inform SPT interval recommendations in order to mitigate the risk for adverse treatment outcomes including TLP.

A recent systematic review on the effects of professional mechanical plaque removal concluded that "the true magnitude of the impact of periodontal maintenance on long-term tooth survival and stability of periodontal parameters has still to be assessed" (Trombelli, Franceschetti, & Farina, 2015). To understand the current state of the evidence, a few factors must be carefully considered: 1) some studies evaluated the influence of SPT on clinical attachment loss (Ramfjord et al., 1982), while others reported tooth loss (Matuliene et al., 2010); 2) of studies which reported tooth loss, very few specifically reported on TLP (Lindhe & Nyman, 1984) which should be investigated as the clinically relevant endpoint of progressive clinical attachment loss; 3) analyzing the frequency of SPT based on the mean number of visits divided by the total follow-up (Farooqi et al., 2015) masks the true impact of non-compliance and ignores inter-patient variability in visit regularity; 4) many earlier studies which set the basis for current SPT recommendations included non-periodontal patients (Axelsson, Lindhe, & Nystrom, 1991; Axelsson, Nystrom, & Lindhe, 2004; Ramfjord et al., 1982); and 5) there is a need for investigating how SPT variables (quantity, regularity, patterns, gap years) interact with the prognostic profile of patients to influence TLP. We attempted to tackle all of these fundamental issues in the present investigation.

Interpretation and clinical significance of our findings

The influence of SPT regularity scales directly with staging and grading

The coefficient of variation (CV) was used as an estimate of SPT regularity in the present study. In the total sample, CV was significantly associated with TLP whereas NMV was not, suggesting that it is not the overall quantity of maintenance visits which deters TLP, but the regularity of visits. Our results demonstrated that patients who visited more regularly for SPT were statistically less likely to experience TLP, and that the impact of regularity directly scaled with disease severity. CV played a significantly larger role in risk of TLP for

This article is protected by copyright. All rights reserved

Author Manuscript

patients with stage III and IV disease as well as for grade C patients. Conversely, CV did not attain significance for stages I and II or grade B patients. This concept is explained graphically in Figure 4 which shows that for stage III/IV patients, TLP events were associated with lower visit regularity, a higher mean number of gap years, and a lower number of annual visits. In comparison, the test and control groups were in close proximity for stages I/II indicating that regularity had less of an influence on risk for TLP for patients with less severe disease. A similar trend can be seen for the grade subgroups.

Altogether, these results provide promising evidence that periodontal maintenance should not be viewed from a "one size-fits all" perspective (Trombelli et al., 2020) and that SPT can be personalized based on patient stage and grade. Furthermore, the present article confirms what was previously found concerning the impact of deep residual PPD following active periodontal therapy as a prognostic factor related to TLP (Loos & Needleman, 2020; Ramseier et al., 2019).

Recommended SPT visit frequency should be modified based on case-specific periodontal risk factors

The optimal frequency for SPT visits should ideally be determined on a case-by-case basis. Periodontal stage and grade provide a useful framework for patient stratification based on a variety of periodontal, radiographic, and systemic parameters (Papapanou et al., 2018). Our analysis involved a unique approach to evaluating SPT where 5-year time periods preceding TLP were compared to random 5-year control periods not associated with TLP for each stage and grade. For our sample, we found that a six-month SPT frequency should be sufficient to mitigate risk of TLP for the vast majority of the population. However, former and current smokers, elderly patients, and diabetics were identified as subpopulations at a higher risk for TLP; for these patients, we recommend a three-month SPT frequency based on previous longitudinal research demonstrating minimal clinical attachment loss at this interval independently of patient oral hygiene and risk factors (Ramfjord et al., 1982; Suomi et al., 1971)

The consequences of missing SPT visits are greater for higher staging and grading

In the present study, the number of years without maintenance ('gap years') in a given 5-year period was used to evaluate the influence of non-compliance on TLP. One gap year in a five-year period had no significant influence on the risk of TLP regardless of stage or grade. However, when multiple gap years were present, there was a significant impact on risk of

This article is protected by copyright. All rights reserved

Author Manuscript

TLP specifically for patients with stage III or IV disease and a strong trend was noted for grade C patients, but not for stages I/II or grades A-B. Figure 3 illustrates how the risk of TLP consistently increases as the number of gap years increases (from 0 to 5). Non-compliant patients with higher staging and grading can clearly be seen to be on a different trajectory regarding risk of TLP.

These results indicate that non-compliance has a comparatively larger impact on risk of TLP for patients with higher-level staging and grading. The consequences of missing SPT visits are greater for patients with more advanced disease and as such, the importance of long-term commitment to periodontal maintenance needs to be emphasized appropriately when patients are diagnosed with stage III/IV or grade C periodontitis.

Limitations of the current investigation

Understanding the limitations of the present article is important in terms of how our conclusions can be extrapolated towards the provision of personalized supportive periodontal therapy in clinical practice. For comparative analyses between control and pre-TLP 5-year periods, stages I-II and III-IV were grouped together. This decision was based on the complexity of case management which is substantially higher for stages III/IV vs. I/II, and also allowed for more powerful analyses. However, this may also be seen as a limitation, as ideally separate analyses should be conducted.

Additionally, our data suggested a stricter maintenance schedule for diabetics, smokers, and elderly patients. How much "stricter" is a question whose answer should be sought by future publications. Furthermore, oral hygiene could not be accurately assessed retrospectively and the decision to extract periodontally involved teeth was made by a range of providers. Finally, the coefficient of variation (CV) was introduced for the first time by the authors and its use for evaluating maintenance regularity needs to be validated in further studies.

Conclusion

Patient stratification based on staging and grading may guide clinicians in personalizing supportive periodontal care. SPT regularity and missing multiple years of maintenance had a larger influence on risk of TLP for higher-level stage and grade. Overall, it is recommended that periodontal patients visit for SPT every six months, and this frequency should be increased for former and current smokers, diabetics, and elderly patients.

This article is protected by copyright. All rights reserved

Author Manuscript

Acknowledgements

This paper was partially supported by the University of Michigan Periodontal Graduate Student Research Fund. All the authors reports no conflict of interest

Author Contributions

Andrea Ravidà*: Contributed to the conception and design of the study, acquisition of the data, and drafting of the article

Matthew Galli*: Contributed to the conception and design of the study, acquisition of the data, and drafting of the article

Muhammad H. A. Saleh: Contributed to the conception and design of the study, drafting of the article, and acquisition of the data

Musa Qazi: Contributed to the acquisition of data

Maria Vera: Contributed to the acquisition of data

Giuseppe Troiano Contributed to the acquisition of data

Hsun-Liang Chan: Contributed towards critical revision of the article and final approval of the version to be published

Hom-Lay Wang: Contributed towards critical revision of the article and final approval of the version to be published

All authors gave final approval and agree to be accountable for all aspects of the work. The asterisk (*) denotes equal contribution to this publication.

Author Manuscript

References

Axelsson, P., Lindhe, J., & Nystrom, B. (1991). On the prevention of caries and periodontal disease. Results of a 15-year longitudinal study in adults. *J Clin Periodontol, 18*(3), 182-189. doi:10.1111/j.1600-051x.1991.tb01131.x

This article is protected by copyright. All rights reserved

Axelsson, P., Nystrom, B., & Lindhe, J. (2004). The long-term effect of a plaque control program on tooth mortality, caries and periodontal disease in adults. Results after 30 years of maintenance. *J Clin Periodontol, 31*(9), 749-757. doi:10.1111/j.1600-051X.2004.00563.x

Becker, W., Berg, L., & Becker, B. E. (1984). The long term evaluation of periodontal treatment and maintenance in 95 patients. *Int J Periodontics Restorative Dent, 4*(2), 54-71.

Chambrone, L., Chambrone, D., Lima, L. A., & Chambrone, L. A. (2010). Predictors of tooth loss during long-term periodontal maintenance: a systematic review of observational studies. *J Clin Periodontol, 37*(7), 675-684. doi:10.1111/j.1600-051X.2010.01587.x

Chapple, I. L. (2014). Time to take periodontitis seriously. *BMJ, 348*, g2645. doi:10.1136/bmj.g2645

Cortellini, P., Buti, J., Pini Prato, G., & Tonetti, M. S. (2017). Periodontal regeneration compared with access flap surgery in human intra-bony defects 20-year follow-up of a randomized clinical trial: tooth retention, periodontitis recurrence and costs. *J Clin Periodontol, 44*(1), 58-66. doi:10.1111/jcpe.12638

Eickholz, P., Kaltschmitt, J., Berbig, J., Reitmeir, P., & Pretzl, B. (2008). Tooth loss after active periodontal therapy. 1: patient-related factors for risk, prognosis, and quality of outcome. *J Clin Periodontol, 35*(2), 165-174. doi:10.1111/j.1600-051X.2007.01184.x

Farooqi, O. A., Wehler, C. J., Gibson, G., Jurasic, M. M., & Jones, J. A. (2015). Appropriate Recall Interval for Periodontal Maintenance: A Systematic Review. *J Evid Based Dent Pract, 15*(4), 171-181. doi:10.1016/j.jebdp.2015.10.001

Graetz, C., Salzer, S., Plaumann, A., Schlattmann, P., Kahl, M., Springer, C., . . . Schwendicke, F. (2017). Tooth loss in generalized aggressive periodontitis: Prognostic factors after 17 years of supportive periodontal treatment. *J Clin Periodontol, 44*(6), 612-619. doi:10.1111/jcpe.12725

Hujoel, P. P., Leroux, B. G., Selipsky, H., & White, B. A. (2000). Non-surgical periodontal therapy and tooth loss. A cohort study. *J Periodontol, 71*(5), 736-742. doi:10.1902/jop.2000.71.5.736

Kornman, K. S., & Duff, G. W. (2012). Personalized medicine: will dentistry ride the wave or watch from the beach? *J Dent Res, 91*(7 Suppl), 8S-11S. doi:10.1177/0022034512449171

This article is protected by copyright. All rights reserved

Author Manuscript

Lang, N. P., Suvan, J. E., & Tonetti, M. S. (2015). Risk factor assessment tools for the prevention of periodontitis progression a systematic review. *J Clin Periodontol, 42 Suppl 16*, S59-70. doi:10.1111/jcpe.12350

Lang, N. P., & Tonetti, M. S. (2003). Periodontal risk assessment (PRA) for patients in supportive periodontal therapy (SPT). *Oral Health Prev Dent, 1*(1), 7-16.

Lindhe, J., & Nyman, S. (1984). Long-term maintenance of patients treated for advanced periodontal disease. *J Clin Periodontol, 11*(8), 504-514. doi:10.1111/j.1600-051x.1984.tb00902.x

Loos, B. G., & Needleman, I. (2020). Endpoints of active periodontal therapy. *J Clin Periodontol, 47 Suppl 22*, 61-71. doi:10.1111/jcpe.13253

Matuliene, G., Studer, R., Lang, N. P., Schmidlin, K., Pjetursson, B. E., Salvi, G. E., . . . Zwahlen, M. (2010). Significance of Periodontal Risk Assessment in the recurrence of periodontitis and tooth loss. *J Clin Periodontol, 37*(2), 191-199. doi:10.1111/j.1600-051X.2009.01508.x

McFall, W. T., Jr. (1982). Tooth loss in 100 treated patients with periodontal disease. A long-term study. *J Periodontol, 53*(9), 539-549. doi:10.1902/jop.1982.53.9.539

Meyer-Baumer, A., Pritsch, M., Cosgarea, R., El Sayed, N., Kim, T. S., Eickholz, P., & Pretzl, B. (2012). Prognostic value of the periodontal risk assessment in patients with aggressive periodontitis. *J Clin Periodontol, 39*(7), 651-658. doi:10.1111/j.1600-051X.2012.01895.x

Ojima, M., Kanagawa, H., Nishida, N., Nagata, H., Hanioka, T., & Shizukuishi, S. (2005). Relationship between attitudes toward oral health at initial office visit and compliance with supportive periodontal treatment. *J Clin Periodontol, 32*(4), 364-368. doi:10.1111/j.1600-051X.2005.00677.x

Papapanou, P. N., Sanz, M., Buduneli, N., Dietrich, T., Feres, M., Fine, D. H., . . . Tonetti, M. S. (2018). Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol, 45 Suppl 20*, S162-S170. doi:10.1111/jcpe.12946

Pepelassi, E. A., Tsiklakis, K., & Diamanti-Kipioti, A. (2000). Radiographic detection and assessment of the periodontal endosseous defects. *J Clin Periodontol, 27*(4), 224-230. doi:10.1034/j.1600-051x.2000.027004224.x

This article is protected by copyright. All rights reserved

Author Manuscript

Pretzl, B., El Sayed, S., Weber, D., Eickholz, P., & Baumer, A. (2018). Tooth loss in periodontally compromised patients: Results 20 years after active periodontal therapy. *J Clin Periodontol, 45*(11), 1356-1364. doi:10.1111/jcpe.13010

Ramfjord, S. P., Morrison, E. C., Burgett, F. G., Nissle, R. R., Shick, R. A., Zann, G. J., & Knowles, J. W. (1982). Oral hygiene and maintenance of periodontal support. *J Periodontol, 53*(1), 26-30. doi:10.1902/jop.1982.53.1.26

Ramseier, C. A., Nydegger, M., Walter, C., Fischer, G., Sculean, A., Lang, N. P., & Salvi, G. E. (2019). Time between recall visits and residual probing depths predict long-term stability in patients enrolled in supportive periodontal therapy. *J Clin Periodontol, 46*(2), 218-230. doi:10.1111/jcpe.13041

Ravida, A., Qazi, M., Troiano, G., Saleh, M. H. A., Greenwell, H., Kornman, K., & Wang, H. L. (2020). Using periodontal staging and grading system as a prognostic factor for future tooth loss: A long-term retrospective study. *J Periodontol, 91*(4), 454-461. doi:10.1002/JPER.19-0390

Rosen, B., Olavi, G., Badersten, A., Ronstrom, A., Soderholm, G., & Egelberg, J. (1999). Effect of different frequencies of preventive maintenance treatment on periodontal conditions. 5-Year observations in general dentistry patients. *J Clin Periodontol, 26*(4), 225-233. doi:10.1034/j.1600-051x.1999.260405.x

Sanz, M., Papapanou, P. N., Tonetti, M. S., Greenwell, H., & Kornman, K. (2020a). Guest Editorial: Clarifications on the use of the new classification of periodontitis. *J Clin Periodontol*. doi:10.1111/jcpe.13286

Sanz, M., Papapanou, P. N., Tonetti, M. S., Greenwell, H., & Kornman, K. (2020b). Guest Editorial: Clarifications on the use of the new classification of periodontitis. *J Clin Periodontol, 47*(6), 658-659. doi:10.1111/jcpe.13286

Suomi, J. D., Greene, J. C., Vermillion, J. R., Doyle, J., Change, J. J., & Leatherwood, E. C. (1971). The Effect of Controlled Oral Hygiene Procedures on the Progression of Periodontal Disease in Adults: Results After Third and Final Year. *J Periodontol, 42*(3), 152-160. doi:10.1902/jop.1971.42.3.152

Tonetti, M. S., Greenwell, H., & Kornman, K. S. (2018). Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. *J Clin Periodontol, 45 Suppl 20*, S149-S161. doi:10.1111/jcpe.12945

This article is protected by copyright. All rights reserved

Trombelli, L., Franceschetti, G., & Farina, R. (2015). Effect of professional mechanical plaque removal performed on a long-term, routine basis in the secondary prevention of periodontitis: a systematic review. *J Clin Periodontol, 42 Suppl 16*, S221-236. doi:10.1111/jcpe.12339

Trombelli, L., Simonelli, A., Franceschetti, G., Maietti, E., & Farina, R. (2020). What periodontal recall interval is supported by evidence? *Periodontol 2000, 84*(1), 124-133. doi:10.1111/prd.12340

World Medical, A. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA, 310*(20), 2191-2194. doi:10.1001/jama.2013.281053

Table and Figure Legends:

Figure 1: Schematic illustration of pre-data processing of pre-TLP 5-year periods and random selection of 5-year control periods. Green color: randomly selected 5-year control periods. Red color: 5-year pre-TLP periods. Purple color: randomly selected 5-year control periods excluded from the analysis due to proximity to tooth loss events. Red box: Limit for randomly selected control periods to be included in the analysis based on proximity to tooth loss events (excluded 5 years before or after).

Figure 2 A-D: Bar graphs illustrating NMV, CV, years without maintenance, as well as downhill patterns, and uphill patterns between control and pre-TLP periods subdivided based on stage I-II (A), stage III-IV (B), grade B (C), and grade C (D).

Figure 3: Graphical representation of how predicted probability of TLP changes with age for patients who missed 0-5 years of SPT during 5-year periods throughout the follow-up.

Figure 4 A-B: The interaction between coefficient of variation for each stage (A) and grade (B) subset over a two-dimensional space with mean number of annual maintenance visits on the x-axis and mean number of gap years (years without maintenance) on the y-axis. Pre-TLP and control 5-year periods were compared throughout the follow-up.

This article is protected by copyright. All rights reserved

Author Manuscript

Table 1: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), and diagnosis in the total population. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.
Table 2: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), and grade in stage I-II and stage III-IV patient subgroups. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

Table 2: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), PPD and BOP after therapy, and grade in stage I-II and III-IV patient subgroups. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

Table 3: Table 3: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), PPD and BOP after therapy, and stage in grade B and C patient subgroups. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

Supplementary Tables

Supplementary Table 1: Analysis of period status (control/pre-TLP) by patterns of maintenance visits over the 5-year period according to stage. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

Supplementary Table 2: Analysis of period status (control/pre-TLP) by patterns of maintenance visits over the 5-year period according to grade. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

Supplementary Table 3: Analysis of period status (control/pre-TLP) by patterns of maintenance visits over the 5-year period for grade B patients only. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age as well as smoking and diabetic status.

This article is protected by copyright. All rights reserved

Author Manuscript

Supplementary Table 4: Analysis of period status (control/pre-TLP) by patterns of maintenance visits over the 5-year period for grade C patients only. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age as well as smoking and diabetic status.

Supplementary Table 5: Detailed summary of analyses performed to substantiate SPT interval recommendations based on patient stage and grade.

Supplementary Table 6: Analysis of period status (control/pre-TLP) by presence of gap years over 5-year periods (one gap vs. no gaps), number of maintenance visits (NMV), regularity (CV), and age for each stage and grade subgroup. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by the age of the patient at the beginning of the period.

Supplementary Table 7: Analysis of period status (control/pre-TLP) by presence of gap years over 5-year periods (multiple gaps vs. one gap), number of maintenance visits (NMV), regularity (CV), and age for each stage and grade subgroup. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by the age of the patient at the beginning of the period.

Author Manuscript

This article is protected by copyright. All rights reserved

Table 1: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), and diagnosis in the total population. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

		OR	95% CI	p-value
	NMV	0.99	0.92 – 1.07	0.799
	CV (%)	1.01	1.00 – 1.02	**0.028***
	AGE	1.03	1.01 – 1.05	**0.001****
	STAGE			**<0.001*****
	I	1		
	II	1.43	0.67 – 3.06	0.353
	III	2.39	1.16 – 4.92	**0.018***
	IV	7.83	3.44 – 17.8	**<0.001*****
	GRADE			**<0.001*****
	A	1		
	B	1.76	0.84 – 3.67	0.135
	C	5.13	2.30 – 11.5	**<0.001*****

*p<0.05; **p<0.01; ***p<0.001

Author Manuscript

This article is protected by copyright. All rights reserved

Table 2: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), PD and BOP after therapy, and grade in stage I-

Stage I-II patients	Stage III-IV patients

Author Manuscript

II and III-IV patient subgroups. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

This article is protected by copyright. All rights reserved

	OR	95% CI	p-value	OR	95% CI	p-value
NMV	0.90	0.78 – 1.04	0.161	0.95	0.85 – 1.06	0.332
CV (%)	0.99	0.98 – 1.01	0.649	1.01	1.00 – 1.01	**0.042***
AGE	1.03	0.99 – 1.07	0.055	1.04	1.02 – 1.06	**0.001****
GRADE			**0.002****			**<0.001*****
A	1			1		
B	1.06	0.40 – 2.82	0.907	10.3	1.59 – 66.6	**0.014***
C	10.3	2.44 – 43.4	**0.001****	24.1	3.68 – 158.1	**0.001****
PD			0.071			**0.001****

Author Manuscript

This article is protected by copyright. All rights reserved

≤4 mm	1			1		
5 mm	2.08	0.79 – 5.43	0.137	2.49	1.54 – 4.05	**<0.001*** **
≥6 mm	-	-	**-**	2.09	1.22 – 3.58	**0.007** **
BOP						
No	1			1		
Yes	1.61	0.91 – 2.84	0.103	1.20	0.71 – 2.02	0.499

*p<0.05; **p<0.01; ***p<0.001

*p<0.05; **p<0.01; ***p<0.001

PPD: probing pocket depth

BOP: bleeding on probing

CV: coefficient of variation

Author Manuscript

This article is protected by copyright. All rights reserved

Table 3: Analysis of period status (control/pre-TLP) by number of maintenance visits (NMV), regularity (CV), PD and BOP after therapy, and stage in grade B

Grade B patients	Grade C patients

Author Manuscript

and C patient subgroups. The results of logistic regression by GEE modelling (OR and 95%CI, p-value) were adjusted by patient age.

This article is protected by copyright. All rights reserved

	OR	95% CI	p-value	OR	95% CI	p-value
NMV	0.96	0.87 – 1.07	0.479	0.91	0.79 – 1.05	0.195
CV (%)	1.01	0.99 – 1.01	0.172	1.01	0.99 – 1.02	0.092
AGE	1.05	1.02 – 1.07	**0.002****	1.02	0.99 – 1.05	0.093
STAGE			**0.035***			**0.003****
I	1			-	-	-
II	1.48	0.38 – 5.82	0.575	1		
III	3.82	1.07 – 13.6	**0.039***	0.46	0.15 – 1.42	0.178
IV	4.01	1.1 – 16.2	**0.031***	2.93	1.03 – 8.9	**0.045***
PPD			**0.001****			0.110
≤4 mm	1			1		

Author Manuscript

This article is protected by copyright. All rights reserved

5 mm	3.07	1.61 – 5.88	**0.001****	1.87	1.03 – 3.39	**0.041***
≥6 mm	3.40	1.72 – 6.50	**<0.001*****	1.91	1.05 – 3.45	**0.039***
BOP						
No	1			1		
Yes	1.37	0.76 – 2.48	0.300	1.43	0.77 – 2.64	0.253

*p<0.05; **p<0.01; ***p<0.001

PPD: probing pocket depth

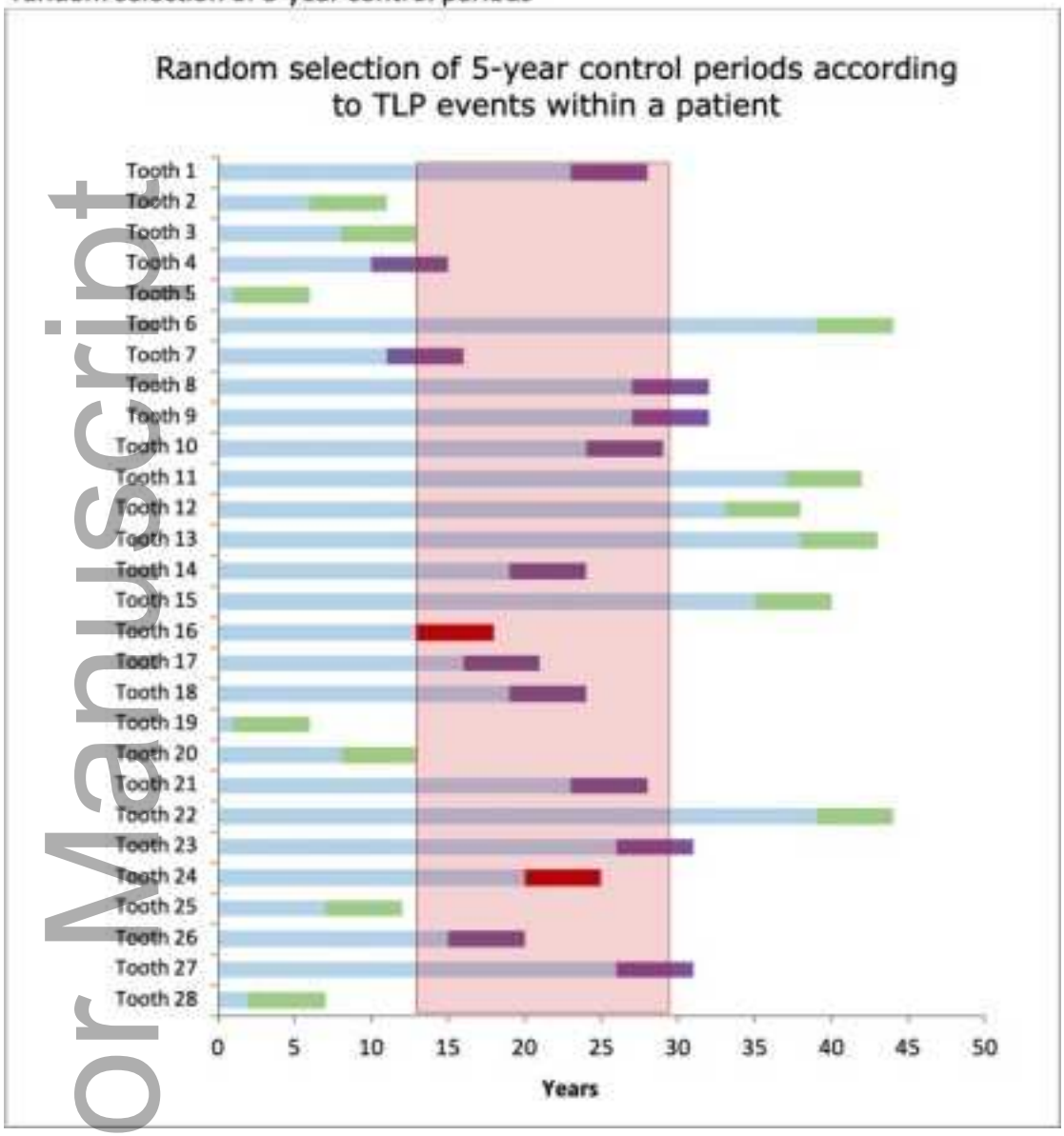
BOP: bleeding on probing

CV: coefficient of variation

Author Manuscript

This article is protected by copyright. All rights reserved

Figure 1: Schematic illustration of pre-data processing of pre-TLP 5-year periods and random selection of 5-year control periods

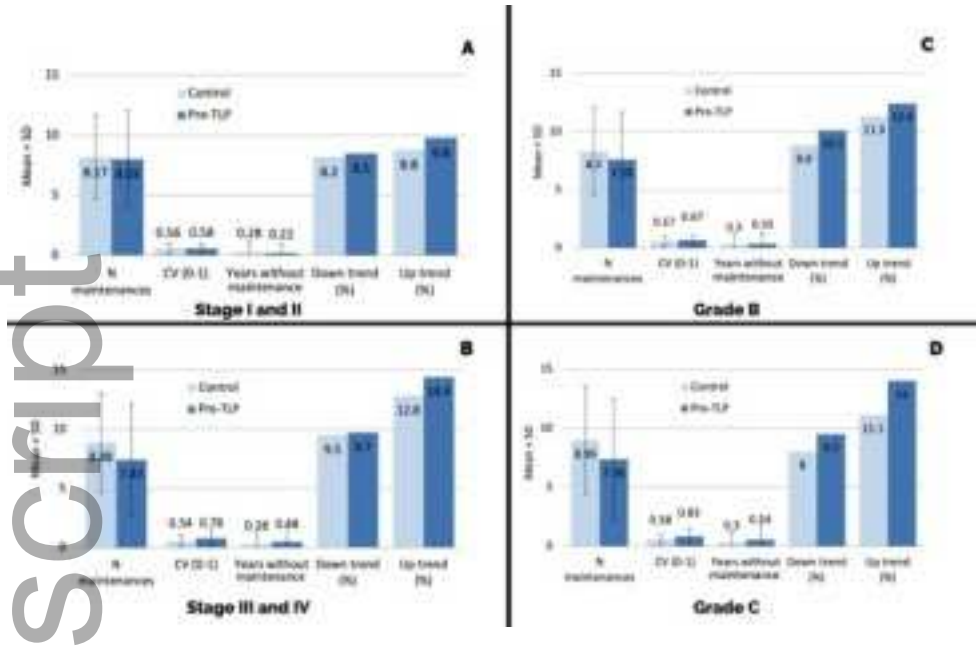


jcpe_13489_f1.tiff

Author Manuscript

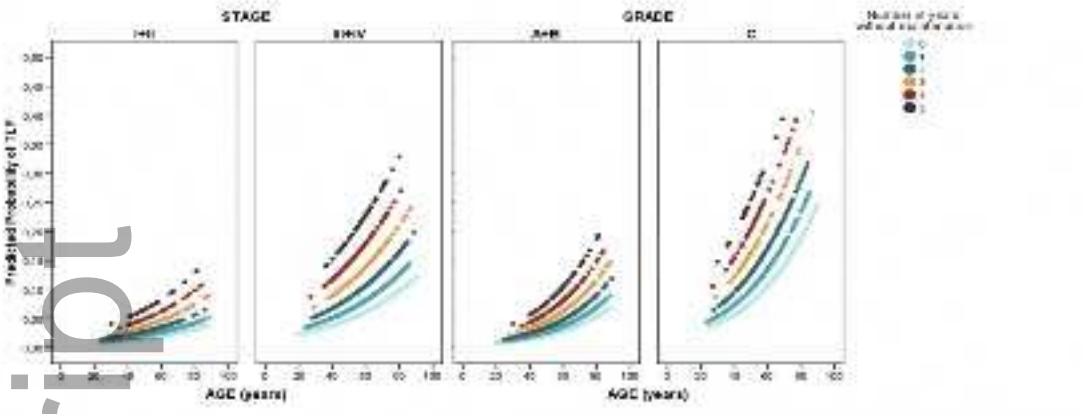
This article is protected by copyright. All rights reserved

Author Manuscript



jcpe_13489_f2.jpg

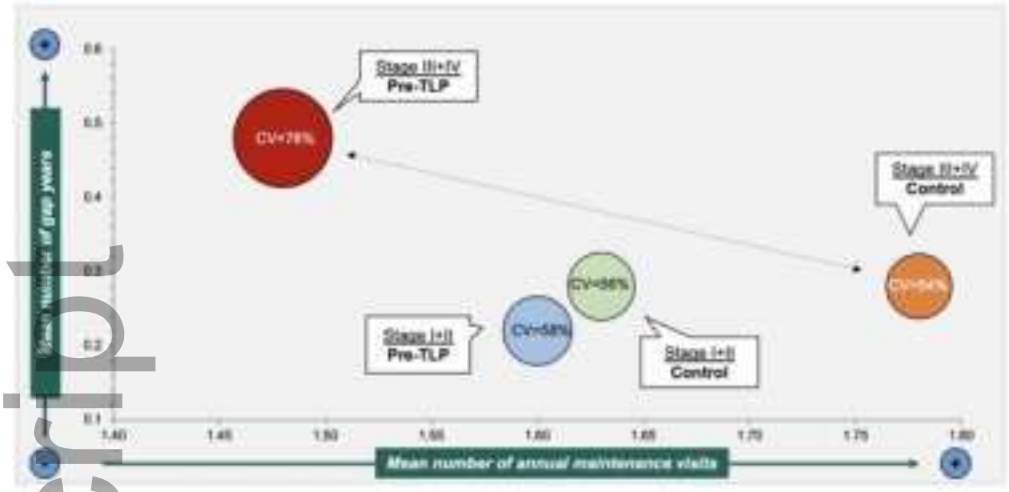
This article is protected by copyright. All rights reserved



jcpe_13489_f3.png

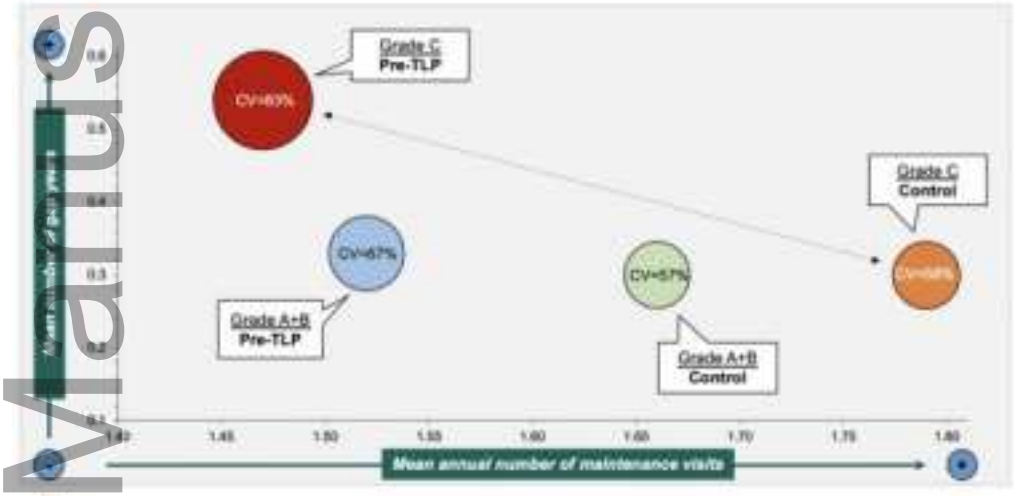
Author Manuscript

This article is protected by copyright. All rights reserved



A

Bubble size is proportional to the coefficient of variation (%)



B

Bubble size is proportional to the coefficient of variation (%)

jcpe_13489_f4.tiff

Author Manuscript

This article is protected by copyright. All rights reserved