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ABSTRACT

Aims: To systematically review the literature to evaluate the recurrence of disease of people in long-term supportive periodontal care (SPC), previously treated for periodontitis, and determine the effect of different methods of managing recurrence. The review focussed on stage IV periodontitis.

Methods: An electronic search was conducted (until May 2020) for prospective clinical trials. Tooth loss was the primary outcome.

Results: Twenty-four publications were retrieved to address recurrence of disease in long-term SPC. Eight studies were included in the meta-analyses for tooth loss, and three studies for disease progression/recurrence (clinical attachment level [(CAL] -loss≥2 mm)). For patients in SPC 5-20 years, prevalence of losing ≥ one tooth was 9.6% (95% confidence interval [CI] 5-14%), whilst experiencing ≥ one site of CAL loss≥2 mm was 24.8% (95% CI 11-38%). Six studies informed on the effect of different methods of managing recurrence, with no clear evidence of superiority between methods. No data was found specifically for stage IV periodontitis.

Conclusions: A small proportion of patients with stage III/IV periodontitis will experience tooth loss in long-term SPC (tendency for greater prevalence with time). Regular SPC appears to be important for reduction of tooth loss. No superior method to manage disease recurrence was found.

CLINICAL RELEVANCE

Scientific rationale for the study: Supportive periodontal care (SPC) is a life-long commitment for the periodontitis patient and for dental professionals taking care of them. Prior to embarking on treatment of periodontitis, patients and dental professionals should understand the likelihood of disease recurrence/progression during SPC and the costs and harms of retreatments during SPC.

Principal findings: Patients in long term routine SPC programmes should expect a low mean prevalence of tooth loss, however disease recurrence/ progression may occur.

Practical implications: The importance of regular SPC recall visits should be emphasised to patients originally treated for stage III/IV periodontitis in order to reduce the risk of tooth loss.

1. INTRODUCTION

Periodontitis is defined as a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and progressive destruction of the tooth-supporting apparatus (Papapanou et al. 2018). It is thought to be the sixth most prevalent condition in the world with severe forms of the disease affecting 7-11% of adults world-wide (Kassebaum et al. 2014, Kassebaum et al. 2017).

Treatment of periodontitis consists of an active periodontal therapy (APT), which often begins with the first step of therapy (Sanz et al. 2020) which includes addressing modifiable risk factors such as tobacco use and glycaemic control in people with diabetes, along with building the skills and behaviours related to effective daily plaque removal (Newton and Asimakopoulou 2018, Carra et al. 2020, Ramseier et al. 2020). Furthermore, when periodontal pockets are established, operative treatments such as non-surgical therapy (subgingival instrumentation - part of the second step of therapy) and surgical options (open flap debridement, resective and regenerative surgery – part of the third step of treatment) are required (Sanz-Sanchez et al. 2020). On completion of APT, ongoing maintenance care, known as supportive periodontal care (SPC) is thought to be essential in minimising disease progression or recurrence (Rosling et al. 2001, Matuliene et al. 2008, Trombelli et al. 2015).

SPC is a complex intervention and may be seen as the fourth step of therapy (Sanz et al. 2020). It is a life-long phase of care, and requires on-going commitment from the patient in order to reduce risk of disease progression and subsequently prevent tooth loss (Lee et al. 2015) and maintain oral health and related quality of life (Armitage and Xenoudi 2016).

Recent systematic reviews have shown that there is limited evidence to advocate the superiority of any one approach to improve tooth maintenance during SPC (Manresa et al. 2018), and that clinical attachment levels (CAL) appear to remain stable over the long term for patients in SPC (Sanz-Martin et al. 2019). Encouragingly, the evidence also suggests that mean annual tooth loss due to periodontitis during SPC of up to 14 years is low (Rosling et al. 2001, Trombelli et al. 2015), however following the 11th European Workshop in Periodontology, it was identified that more research was required to plug

gaps in the evidence, particularly regarding treatments which work best in the phase of SPC (Sanz et al. 2015). A conclusion strengthened by a recent Cochrane review (Manresa et al. 2018).

What is less clear from previous reviews is what patients might expect in terms of recurrence of the condition and the effect of different treatment methods of managing recurrence, which may be considered in terms of stabilising recurrence and preventing tooth loss, associated costs and effect on quality of life.

Thus, in view of the gaps in the evidence and its importance both from a public health consideration as well as the perspective of the individual patient, the purpose of this systematic review was to 1) systematically review the evidence for the recurrence of periodontitis during long term supportive periodontal care; and 2) to identify the effect of different methods of managing recurrence.

1.1 Objectives

1.1.1 Focussed Questions (FQ)

The two questions which we sought to answer were focussed question 1 (FQ-1): 'In people treated for periodontitis and in SPC for five years or more, compared with no or irregular SPC, how common is recurrence of the condition?' and, focussed question 2 (FQ-2): 'In people experiencing recurrence of periodontitis, what is the effect of different methods of treatment of the recurrence as assessed by measures of health, quality of life, cost and accessibility of care and harms?'.

1.1.2 PICOS Components

Population

Participants treated for periodontitis with no age restriction. Any definition of periodontitis was included considering there have been a number of changes in the classification of periodontal diseases over recent decades. No restriction was applied for the type of treatments carried out both in the APT or supportive periodontal care phases. The end of active treatments was clearly defined in terms of periodontal health status. The focus of the workshop for which this review was commissioned was stage IV periodontitis (advanced disease with extensive tooth loss) (Tonetti et al. 2018). However, in view of

both the recent adoption of this classification and our expectation that severity of periodontitis would be incompletely described, we included all severities of periodontitis with a plan to analyse stage IV periodontitis separately if possible.

Intervention

Any kind of intervention that might be considered part of SPC. As SPC is a complex intervention, for the purposes of this review this may have included;

- Interview: periodontal health symptoms, medical and social history, risk factors including tobacco use, stress and diabetes and reported plaque control regime
- Assessment: plaque and calculus deposits, periodontal health including inflammation, probing pocket depths and bleeding pockets
- Formulating: intervention needs including risk factor management, oral hygiene and retreatment
- Practical Intervention: oral hygiene coaching, instrumentation of supra- and subgingival plaque and calculus, treatment of sites with recurrence (finding of periodontitis at a previously healthy/stable site) or residual periodontitis (a deep periodontal pocket remains despite active therapy) (Graziani et al. 2018).
- Planning: interval before next SPC visit

Comparison

Studies comparing SPC with no/irregular SPC, different frequencies of SPC recall visits, different settings for SPC (specialist versus non-specialist) and SPC using adjuncts (e.g. chemical agents, locally administered antiseptics/ antibiotics and systemically administered antibiotics).

Outcome Measures

It would be impossible to distinguish the published literature between recurrence, occurrence of disease at previously healthy (non-diseased) sites and progression of residual disease at unstable sites. Recurrence means a finding of periodontitis at a site that was rendered periodontally healthy/ stable through treatment. Occurrence refers to a site within a patient diagnosed and treated for periodontitis (periodontitis case) but which did not previously show signs of disease, and progression would be characterised by deterioration (e.g. CAL loss) at a site that had residual disease despite active treatment.

Since we could not make the distinction from the existing literature, the primary outcome measure for this systematic review was the proportion of patients who experienced tooth loss. Secondary outcomes were 1) proportion of patients whom experienced at least one site of CAL loss of 2 mm or greater; 2) number of periodontal probing pocket depths (PPD) of at least 5 mm or more with bleeding on probing; 3) number of sites that need/ experienced retreatment; 4) change in oral health related quality of life (OHQOL) with a validated OHQOL tool; 5) health economic outcomes; 6) any other patient reported outcomes (PRO).

Study Design

The search strategy included clinical studies with a prospective design (for both FQ-1 and FQ-2) in order to minimise selection bias. As FQ-2 was an intervention research question, studies were limited to randomised controlled trials, controlled trials and prospective cohorts.

2. METHODS

2.1 Protocol Development and Registration

This protocol was evaluated and approved by the Scientific Committee of the XVII European Workshop on Periodontology and was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al. 2009). Details of the protocol for this systematic review were registered on PROSPERO (Unique ID: CRD42020176451).

2.2 Patient Involvement

This review was co-produced with a member of the British Society of Periodontology Patient Forum who contributed to design, interpretation and publication.

2.3 Eligibility Criteria

To conduct this systematic review, we searched for all studies which had included treatment for periodontitis and had a minimum of 5 years following the end of the APT.

2.4 Literature Search

2.4.1 Electronic Search

A sensitive search strategy was formulated with an experienced librarian (DM) with consideration of previous systematic reviews related to this topic (Trombelli et al. 2015, Manresa et al. 2018, Sanz-Martin et al. 2019) using a string of medical subject headings and free-text terms (see Appendix S1-S6). The search strategies were modelled on that devised for the MEDLINE database and subsequently modified for other databases as was needed. The search was restricted to the English language (to harmonise methods across all reviews being conducted for the European Workshop and due to time constraints) and results were downloaded to EndNote X9 (2013).

Electronic databases searched included;

Ovid MEDLINE (1946 -1 May 2020) (Appendix S1);

Ovid EMBASE Classic and EMBASE (1947 – 1 May 2020) (Appendix S2);

LILACS VHL Regional Portal (to 2 May 2020) (Appendix S3);

Cochrane Central Register of Controlled Trials (CENTRAL) (to 2 May 2020) (Appendix S4);

Dentistry and Oral Sciences Source EBSCOHost (to 2 May 2020) (Appendix S5);

CINAHL Plus EBSCOHost (1937 – 2 May 2020) (Appendix S6)

OpenGrey was searched for grey literature and the register of clinical studies at the US National Institutes of Health (www.clinicaltrials.gov) in order to identify unpublished studies which may be relevant.

2.5 Study Selection

2.5.1 Inclusion Criteria

In regard to FQ-1, the following inclusion criteria were applied:

- prospective studies (to minimise the risk of selection bias)

- minimum follow-up of 5 years in SPC (to consider outcome of disease progression/ recurrence)
- endpoint of APT and the start of SPC clearly defined

For FQ-2, the following inclusion criteria were applied:

- prospective studies
- minimum follow-up of 12 months

2.5.2 Exclusion Criteria

The following exclusion criteria were applied:

- Cross-sectional studies
- Retrospective studies
- Case- series

  To distinguish between case-series and cohort studies (particularly with low numbers of participants), a key characteristic for exclusion was a lack of information on the method of enrolment/ participant selection (e.g. consecutive cases).
- Studies which investigated solely specific systemic disease or risk factors (e.g. smoking, diabetes) or only recruited participants for periodontitis treatment or previously treated for periodontitis

2.5.3 Screening

Titles and abstracts (if available) retrieved from the searches were screened by a combination of two review authors (NL, FM and SH), in duplicate and independently. Based on titles and abstracts, irrelevant studies were discarded. Full texts were obtained for the remaining studies and included those which had insufficient information in the title and abstract and if at least one reviewer included the study for the next phase of screening. Reference lists of all studies that were included for full text screening and previous reviews were screened for missing records.

Two reviewers (NL and FM) assessed the full text reports according to the inclusion criteria, in duplicate and independently. Disagreements were resolved by discussion and a third author was consulted (IN) when agreement could not be resolved. Where there were several publications from the same original study, we included the study with the

longest follow up period for the relevant outcome measure. Studies that did not meet the eligibility criteria were excluded and specified reasons for exclusion (Appendix S7).

2.6 Data Collection

2.6.1 Data Extraction

Data were extracted by two review authors (NL and FM), in duplicate and independently using a data extraction form on Microsoft® Excel. Disagreements were resolved by discussion and when resolution was not possible, a third reviewer was consulted (IN). In order to clarify missing or unclear data, authors were contacted (where possible).

2.6.2 Risk of Bias

Quality assessment was carried out by two review authors (NL and SH), in duplicate and independently. Regarding FQ-1, studies were assessed for risk of bias in relation to the phase of SPC. The included studies were assessed as prospective cohorts using a modified version Newcastle-Ottawa scale (NOS) (Wells et al. 2011) to account for single arm cohorts. The modified version of the NOS removed questions concerning control groups, therefore two domains, selection and outcome, were assessed with a maximum score possible of six. FQ-2 included studies were assessed for risk of bias using the Cochane RoB 2.0 tool (Sterne et al. 2019) for interventional randomised controlled trials (RCT), ROBINS-I tool (Sterne et al. 2016) for interventional non-randomised controlled trials (CCT) and cohorts.

2.7 Data Synthesis

Data were entered into tables stratified by study design, and decisions on which studies to include in a meta-analysis was made depending on the similarity of chief study characteristics related to each research question (i.e. incidence of recurrence or methods of managing recurrence).

Evaluation of the included studies displayed substantial heterogeneity between publications in regard to design and reporting of outcomes in the SPC phase and in trials addressing treatment methods for disease recurrence. A qualitative report of the data was planned for those studies that could not be included in the meta-analyses.

2.8 Data Analysis

The number of events on the total number observed at the final assessment was used for the meta-analyses. To avoid under-estimating both tooth loss and CAL loss≥2 mm, we decided to use the 'per protocol' number of participants. Numerous studies reported tooth loss per participant at the end of the study. An intention to treat approach would not be able to account for tooth loss associated with subjects during follow up, and thus risk under-estimating average tooth loss. In order to check this, an intention to treat analysis (ITT) was carried out for the primary outcome of tooth loss.

Data were grouped with respect to a) frequency of SPC, 3 monthly (3M) or unmonitored/irregular (IRREG) and; b) length of follow-up (FU), 5-10 years follow-up (5-10 FU) or greater than 10 years follow-up (>10 FU). Meta-analyses were subsequently performed to determine an overall prevalence of tooth loss (primary outcome) and CAL loss (≥2 mm) (secondary outcome) at patient level. The number of events on the total number observed (per protocol) were entered into the statistical software. In regard to tooth loss, this was the number of patients who lost at least one tooth, on the total number of patients available at follow-up. For CAL loss, this was the number of patients experiencing CAL loss≥2 mm at a minimum of one site, on the total number of patients available at follow-up. In the meta-analyses, 'clusters' were formed in each subgroup (Salvi et al. 2018). One cluster was representative of one treatment arm in APT. Therefore, studies with multiple treatment arms, contributed more than one cluster. Open source software, OpenMeta[Analyst] (Wallace et al. 2012), was used for meta-analysis, and a binary random-effects model chosen. Weighted mean values and 95% confidence intervals (CI) are presented via Forest plots. A p value of <0.05 was considered statistically significant.

The degree of statistical heterogeneity between studies was assessed using the chi-square test and quantified utilising the I^2 statistical test. Subgroup and meta-regression analyses were performed to determine the effect of: a) the type of treatment in APT either regenerative (reg) or non-regenerative (non-reg), b) frequency of SPC, 3 monthly or IRREG and; c) length of follow-up, 5-10 years or greater than 10 years on tooth loss and CAL loss ≥2 mm and expressed as coefficients (COEF) and 95% confidence intervals. Meta-analysis was stratified into subgroups of reg and non-reg surgery to allow

evaluation of potential differences in outcomes. The summary estimate includes both types of therapy combined.

Interpretation of the I^2 test was according to the guidance of the Cochrane Handbook (Deeks et al. 2019), as follows:

- 0% to 40%: might not be important
- 30% to 60%: moderate heterogeneity
- 50% to 90%: substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Studies that could not be included in the meta-analysis were described in a narrative form and an attempt to triangulate qualitative results with that of the meta-analysis was made to assess consistency of data.

Kappa statistic was used to assess the reviewer agreement based on full-text screening, and the score interpreted using values suggested by Cohen (1960). The reviewers were calibrated with the first 10 full text publications.

3. RESULTS

3.1 Study Selection

The search yielded a large number of records, confirming a high sensitivity and low specificity which reflected the search strategy. Based on the definition of stage III versus stage IV periodontitis (Tonetti et al. 2018), we were unable to restrict the studies to solely stage IV periodontitis cases. Studies screened gave no detail of reasons for previous extraction(s) and most used previous classifications for defining included cases. Additionally, there was a lack of studies which specifically addressed recurrence in SPC.

A total of 31,303 records were found through the electronic searches, and following removal of duplicates, 14,860 remained (Figure 1). Following screening of titles and abstracts, 228 titles remained for full-text evaluation. Subsequently, 204 studies were

excluded (Appendix S7) for often more than one reason, however the main reason was generally recorded.

FQ-1

24 studies (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Hou et al. 1997, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Crespi et al. 2011, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020) were included in the qualitative and quantitative analysis (Tables 1 and ~~Table~~ 2).

Studies reporting on the same population were included if each paper reported on a different but relevant outcome important for this systematic review (Pihlstrom et al. 1984, Kaldahl et al. 1996b) (Table 2). The kappa score for FQ-1 was calculated to be 0.81 for full-text screening agreement indicating almost perfect agreement (Cohen 1960).

FQ-2

Six studies were included (Jenkins et al. 2000, Bogren et al. 2008, Lulic et al. 2009, Tonetti et al. 2012, Costa et al. 2015, Killeen et al. 2018) (Tables 3 and ~~Table~~ 4). These were qualitatively analysed due to heterogeneity particularly in types of intervention. The kappa score for full-text screening for FQ-2 was calculated to be 0.62 indicating substantial agreement (Cohen 1960).

3.2 Population

We were unable to find data on stage IV periodontitis or that could be analysed as such. Studies reported an initial diagnosis of periodontitis with some further describing as moderate and severe disease. Types of diagnosis reported in the articles included, ‘advanced periodontal disease’, ‘moderate to advanced adult periodontitis’, ‘aggressive periodontitis’, ‘chronic periodontitis’, ‘advanced chronic periodontitis’, and ‘severe chronic periodontitis’. One recently published study (Cortellini et al. 2020) referred to the population as, ‘stage III or IV periodontitis’ in a retrospective manner, as recruitment was prior to the publication of the most recent classification (Table 1).

3.3 Supportive Periodontal Care

3.3.1 Description of SPC

When assessing the elements carried out in the phase of SPC, the majority of studies included brief description of oral hygiene review and re-enforcement in conjunction with focussed supra- and subgingival instrumentation (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Hou et al. 1997, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Crespi et al. 2011, Dori et al. 2013, Cortellini et al. 2017). Five publications did not describe any detail about recall visits (Knowles et al. 1979, Moder et al. 2012, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020).

Nine studies provided some description of the operator(s) who carried out the SPC visits (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1984, Rosling et al. 2001, Loesche et al. 2002, Loesche et al. 2005, Nygaard-Ostby et al. 2010, Cortellini et al. 2017, Cieplik et al. 2018) although level of experience was not advised.

No studies specifically addressed risk factor control in regard to smoking cessation or glycaemic control advice. Details of the factors which influenced recall interval length were not given in any study.

3.3.2 Recall Intervals

All studies reported on the frequency of recall intervals, with the majority of studies applying 3 monthly visits. However, there was some variability between studies, with the shortest interval being 1-3 months (Hou et al. 1997) and the longest being up to 12 months (Rosling et al. 2001), based on a perceived disease risk by the attending dentist (details not specified). Some studies reported a more frequent recall plan in the first 1-2 years after APT (Axelsson and Lindhe 1981, Buchmann et al. 2002, Moder et al. 2012, Cieplik et al. 2018), thereafter reducing the frequency with tailored SPC intervals.

3.3.3 Length of Follow-Up

The minimum follow-up period in SPC to be included in this review was 5 years. Seventeen studies had a follow-up of 5-10 years (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996a, Kaldahl et al. 1996b, Hou et al. 1997, Becker et al. 2001, Serino et al. 2001a, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2020). Seven studies (Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001b, Crespi et al. 2011, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019) had SPC follow-up periods greater than 10 years. Two studies reported on 20 years of follow-up (Cortellini et al. 2017, Petsos et al. 2019).

3.4 Meta-Analyses

3.4.1 Tooth Loss

Eight studies addressing FQ-1 contributed data for estimating tooth loss at patient level (Orsini et al. 2008, Nygaard-Ostby et al. 2010, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020). Data were sub-grouped according to treatment arms in APT, culminating in a) six clusters for patients in the 3M subgroup and seven clusters in the IRREG subgroup; and b) seven clusters for patients in the 5-10 FU subgroup and six clusters in the >10 FU subgroup. The per protocol meta-analysis at patient level for tooth loss, observed 192 participants (Figure 2).

The 3M subgroup included 98 participants, whilst the IRREG subgroup observed 94. The proportion of patients experiencing tooth loss overall yielded a weighted value of 9.6% (95% CI 5-14%), with low heterogeneity I^2=28% (p=0.161). Subgroup analysis showed a weighted mean value for the 3M group as 8% (95% CI 2-14%), with low-moderate heterogeneity I^2=32% (p=0.195), whilst the IRREG group displayed a 11.9% (95% CI 5 - 19%) prevalence, low-moderate heterogeneity I^2 30.2% (p=0.198).

The ITT meta-analysis included a total of 218 participants (Appendix S8). The 3M subgroup had 107 patients, and the IRREG subgroup included 111. As anticipated, the percentages were less than the per protocol analysis. Overall, the proportion of patients

experiencing tooth loss was 8.3% (95% CI 4.3-12.3%) and low heterogeneity (I^2=24%, p=0.197). The subgroup analysis found that the 3M group displayed a prevalence of 7.3% (95% CI 1.8-12.8%) and low heterogeneity, I^2=28% (p=0.223), whilst the IRREG group was 9.9% (95% CI 3.6-15.1%) with low heterogeneity once again, I^2=29% (p=0.207).

Length of follow-up time was also considered at patient level for tooth loss (Figure 3), 106 participants were observed in the 5-10 FU subgroup and 86 in the >10 FU subgroup. The weighted value for tooth loss was 8.2% (95 CI 3%-13%) for the 5-10 FU group and 12.7% (95% CI 4-22%) for >10 FU group, with substantial heterogeneity I^2 test 70% (p=0.374) and 51% (p=0.070) respectively.

The ITT analysis according to follow-up time at patient level (Appendix S9) observed 124 participants in the 5-10 FU subgroup and 94 in the >10 FU subgroup. The proportion of patients experiencing tooth loss for the 5-10 FU group was 7.3% (95% CI 2.9-11.7%) and for the >10 FU group was 11.5% (95% CI 3.2-19.9%), with no heterogeneity detected I^2=0% (p=0.453) and substantial heterogeneity I^2 test 50% (p=0.073) respectively.

Meta-regression analyses were performed to investigate the influence of type of treatment in APT (regenerative or non-regenerative), frequency of SPC (3M or IRREG) and length of follow-up (5-10 FU or >10 FU) on tooth loss. There was no evidence of an association between type of treatment (COEF 0.1; 95% CI -0.07 – 0.3, p=0.249), frequency of SPC (COEF 0.05; 95% CI - 0.05 - 0.1, p=0.341) or length of follow-up (COEF 0.02; 95% CI -0.08 – 0.1, p=0.704) and tooth loss was found.

3.4.2 Clinical Attachment Level loss (≥2 mm)

Three studies for FQ-1 contributed data for estimating the number of patients experiencing CAL loss ≥2 mm (Dori et al. 2013, Cortellini et al. 2017, Petsos et al. 2019). Data were sub-grouped according to treatment arms in the APT, culminating in a) three clusters for patients in the 3M subgroup and four clusters in the IRREG subgroup; and b) two clusters for patients in the 5-10 FU subgroup and five clusters in the >10 FU subgroup. The meta-analysis for patients experiencing CAL loss ≥2 mm, observed 86 participants (Figure 4).

The 3M subgroup observed 41 participants, whilst the IRREG subgroup observed 45. The proportion of patients experiencing at least one site of CAL loss≥2 mm overall yielded a weighted mean value of 24.8% (95% CI 11-38%), with substantial heterogeneity I^2 =63% (p=0.013). Subgroup analysis showed a weighted mean value for the 3M group as 30.2% (95% CI -2-63%), I^2 = 87% (p<0.0001), whilst the IRREG group displayed a 21.4% (95% CI 100.1% -330.3%) prevalence, I^2 0% (p=0.884). The difference between the groups was not statistically significant (p=0.332).

Length of follow-up time was assessed at a patient level for CAL loss ≥2 mm (Figure 5), with 22 participants observed in the 5-10 FU subgroup and 64 in the >10 FU subgroup. The proportion of patients experiencing at least one site of CAL loss ≥2 mm was 22.1% (95% CI 5-39%) for the 5-10 FU group and 26.3% (95% CI 8-45%) for >10 FU group I^2 = 0% (p=0.609) and 75% (p=0.003) respectively.

The random effects meta-regression analyses found no association between frequency of SPC (COEF 0.13; 95% CI -0.1 – 0.4, p=0.332) and length of follow-up (COEF -0.16; 95% CI -0.5 – 0.2, p=0311) with percentage of patients experiencing CAL loss≥2 mm, however the type of treatment carried out in APT (regenerative or non-regenerative) was significantly associated (COEF 0.26; 95% CI 0.01 – 0.5, p=0.043), whereby a non-regenerative intervention was more likely to experience greater proportion of patients with CAL loss≥2 mm. Therefore, the estimate of the prevalence of patients with CAL loss≥2 mm would be expected to increase by 0.26 when non-regenerative treatment was carried out in APT according to this random effects meta-regression model.

3.5 Qualitative Analyses

3.5.1 Tooth Loss

FQ-1

Tooth loss was reported in 17 studies, however due to substantial heterogeneity in reporting of this outcome, nine studies could not be included in the meta-analyses (Axelsson and Lindhe 1981, Pihlstrom et al. 1984, Kaldahl et al. 1996a, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Loesche et al. 2002) and are described in a narrative form (Appendix S10).

One study (Loesche et al. 2002) with regular 3 monthly SPC and a follow-up of a median of 61.2 months, reported the proportion of patients with tooth loss as being 56.8%. This is substantially higher than that estimated for the 3M subgroup analyses (8.0%, 95% CI 1.9-14.1%) and 5-10 FU subgroup (8.2%, 95% CI 3.0-13.4%). Additionally, the authors reported a substantial drop out rate of 46 participants from the original 90 subjects who entered the maintenance phase. On the other hand, one other small split-mouth study (Becker et al. 2001) reported the prevalence as 0% over the course of 5 years.

A number of studies reported mean tooth loss over the course of SPC (Axelsson and Lindhe 1981, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b). Some studies did not report the reasons for extraction and, so as to prevent under-estimation of tooth loss, were included in the summary (Appendix S10). Other studies reported absolute numbers of teeth lost (Pihlstrom et al. 1984, Kaldahl et al. 1996a).

For studies with a 5-10 FU (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Becker et al. 2001, Serino et al. 2001a, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005), average tooth loss per patient ranged from 0 - 2.6 teeth, whilst for studies with >10 FU (Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001b), this ranged from 0.6 (±1.1) to 2.7 (±3.7) teeth per patient.

Studies which performed regular 3-4 monthly SPC (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Loesche et al. 2002, Loesche et al. 2005) reported mean tooth loss ranging from 0 to 2.7 or absolute numbers of teeth lost (from the cohort) in the range of 8 - 46 (+2 roots) over the course of SPC.

FQ-2

One RCT (Bogren et al. 2008) and one prospective cohort (Costa et al. 2015) reported on tooth loss in patients previously treated for moderate to advanced periodontitis in SPC with unstable disease (Appendix S11).

Bogren et al. (2008) compared locally delivered 8.8% doxycycline gel applications (every 3 months) with scaling and root planing (SRP) in 63 participants (test) in sites of PPD≥5 mm to SRP alone (control) in 65 participants. The study reported 25 lost sites due to tooth extraction (mean of 0.4 sites/participant) in the test group compared with 45 lost sites (mean 0.7 sites/ participant) in the control group over a 3-year follow-up period with routine 6 monthly SPC. The difference was not statistically significant ($p>0.05$) between treatment groups.

A prospective cohort study (Costa et al. 2015) analysed a population of 212 individuals over a 5-year period and retrospectively divided the cohort into two groups according to SPC visit compliance. 96 regular compliers (RC) and 116 IRREG compliers (IC) were subject to non-surgical therapy (NST) and, if deemed necessary, surgical therapy (ST) (if persistent PPD≥5 mm were detected). Mean tooth loss was reported to be 0.6 and 0.8 for RC and IC respectively. The difference was found to be statistically significant ($p<0.05$). Tooth loss was also assessed according to treatment modality within each compliance group. The RC group demonstrated a mean tooth loss of 0.3 (NST) and 0.8 (ST), compared with the IC group, which was 2.2 and 2.8 for NST and ST respectively. The differences between groups for both NST and ST were statistically significant. Interestingly, in both RC and IC groups, ST influenced greater tooth loss after 5 years.

3.5.2 Sites with CAL loss≥2 mm

FQ-1

The majority of studies reported mean or median CAL over the duration of SPC. Some studies reported sites experiencing mean CAL loss≥2 mm as frequency distributions at various timepoints in SPC or in relation to initial PPD (prior to APT).

One study (Buchmann) of 13 participants reported the prevalence of disease progression over a 5 year follow-up at various timepoints. This study reported total of 64 sites which experienced disease progression and it was not clear whether these sites were recurrent or newly occurrent. The greatest number of sites experiencing disease progression occurred at 60 months, where 17 sites (18.3%) experienced CAL loss≥2 mm, followed by 12 sites (16.3%) which occurred at 36 months.

Another study (Kaldahl et al. 1996b) reported 'breakdown' sites where attachment loss was ≥3 mm. This group found a mean incidence per year of 1.24% over the course of 84 months of routine 3 monthly SPC. Of interest, a small proportion of participants (10%) accounted for a mean of more than 3.0% incidence per year, and these were all smokers.

Moder et al. (2012) conducted a split mouth study over 72 months of SPC and reported a total of 14 sites lost less than or equal to 2 mm of attachment. It should be noted that some sites may have lost less than 2 mm of attachment, however, we were unable to extract this information.

Finally, one study with 64 participants with a follow up of 144 months in SPC reported mean annual proportions of sites showing 2 mm attachment loss with respect to baseline PPD (Table 2) (Ramberg et al. 2001). The greatest mean proportion was consistently seen in the PPD≥6 mm category for the SRP group which was 7.5% (±6.4) between 12 and 36 months, 7.8% (±8.7) from 36-60 months and 2.9% (±8.2) between 60 and 156 months of SPC.

FQ-2

Two studies reported on the sites with CAL loss≥2 mm (Jenkins et al. 2000, Tonetti et al. 2012) and both trials reported no statistically significant difference between test and control groups (Appendix S11).

One controlled clinical trial (CCT) (Jenkins et al. 2000) assessed 17 patients (146 sites) in a coronal scaling (CS) group versus 14 patients (130 sites) in a subgingival scaling (SS) over a 12 month period. Participants whom previously had been treated for periodontitis and entered SPC, presented with at least 4 pockets of PPD ≥4 mm. The appropriate intervention was delivered at baseline, 3, 6 and 9 months. The authors reported 21 of these 'loser' sites (defined as CAL loss≥2 mm) in each group, and no statistically difference between groups was found. Initial PPD ≥6 mm demonstrated a greater proportion of sites that were 'loser' sites, 28.6%, compared to 11.6% of those with initial PPD 4-5.9 mm for the SS group. The corresponding proportions for the CS group were 20.5% (initial PPD≥6 mm) and 11.8% (initial PPD 4-5.9mm). The authors

concluded that the risk of attachment loss was greater if the initial PPD was 6mm or above, however this was only statistically significant for the SS group.

Tonetti et al. (2012) reported on 202 subjects in a multicentre RCT, comparing SRP and a single adjunctive 14% doxycycline gel application to SRP alone with a follow-up of 12 months. Participants had previously been treated for periodontitis and presented with at least four teeth with residual PPD ≥5 mm and a positive BOP. SPC was performed every 3 months for 1 year. A total of 15 participants (7.5%) experienced CAL loss≥2 mm (8 test, 7 controls). No statistically significant difference between groups were reported for any parameters at the 12 months.

3.5.3 Pockets of 5 mm or More with Bleeding on Probing

No studies reported specifically on the number of pockets of ≥5 mm with bleeding on probing during the SPC phase, but some reported on the proportion of sites within specific PPD categories. Additionally, for treatment of recurrence in SPC, the mean number of sites with PPD≥5 mm were reported without mention of bleeding on probing (Bogren et al. 2008, Tonetti et al. 2012).

3.5.4 Sites That Need/ Experience Retreatment

Kaldahl et al. (1996b) reported at total of 685 breakdown sites (461 from the SRP, Modified Widman Flap (MWF) and osseous recontouring groups) during the course of SPC that required re-treatment. From this, 5-12% of breakdown sites (experienced ≥3 mm attachment loss) which were subsequently re-treated, experienced further loss of attachment.

3.5.5 Oral Health Related Quality of Life (OHQoL)

The only study that reported on OHQoL was Cortellini et al. (2020). This study used the Italian translation of the Oral Health Impact Profile (OHIP)-14 questionnaire at baseline, 1, 5 and 10 years after treatment. One year after regenerative treatment (the first reassessment after APT), the mean OHIP-14 score was 6.6 (±2.4) and this was compared to a rehabilitated group (not relevant to this review). No data were reported at 10-years.

One study (Cortellini et al. 2017), reported recurrences that required retreatment. These recurrences occurred in all three treatment groups, MWF, modified papilla preservation technique (MPPT) with expanded-polytetrafluroethylene membrane (e-PTFE) and flap with e-PTFE. A total of 26 recurrences occurred in 20 years where sites of PPD≥5 mm at the 1-year reassessment, showed the highest frequency of recurrence that required re-intervention.

3.5.6 Health Economic Outcomes

Two studies (Cortellini et al. 2017, Cortellini et al. 2020) reported total cumulative costs for operative interventions. This cost calculation included actual cost of the procedures (using average fees from nine practices in Italy), all complications experienced which required re-treatment, and included tooth loss. Cortellini et al. (2020) reported (in graphical form) that the cumulative costs for a regenerative procedure over 10 years, amounted to a mean of just over €2500, however SPC appointments were not included in this calculation. The cumulative costs over a 20 year period (including 3 monthly SPC) ranged from a mean of €3090.98 (±210.66) to €3382 (±88.95), depending on the initial surgical therapy (Cortellini et al. 2017).

3.5.7 Other Patient Reported Outcomes (PRO)

One study (Kaldahl et al. 1996a) reported on the occurrence of periodontal abscesses in the context of the therapy type in APT, over the 84 month follow-up. Twenty-seven abscesses were reported, with 23 episodes (85%) occurring in the group originally treated by coronal scaling alone. Deep probing depths (≥7 mm) at the initial examination was associated with 17 abscesses (63%).

Masticatory function and aesthetics were assessed by Cortellini and co-workers (Cortellini et al. 2020). A 5-point Likert scale was utilised to assess changes from baseline to 10 years. The authors report that between the one and ten-year follow-up period, the proportion of participants with ‘no concern’ in regard to masticatory function remained stable. Those reporting, ‘some concern’ appears to increase over the 9 years of SPC (graphical information available only). A similar scale was used for assessing aesthetics, and once again, whilst those reporting ‘no concern’ appears to remain stable

between the one and ten-year follow-up, those reporting 'some concern' appears to increase over the follow-up.

Two studies reported on adverse events in the context of experimental treatment groups (Jenkins et al. 2000, Tonetti et al. 2012). Jenkins et al. (2000) reported no adverse events in relation to coronal and subgingival scaling. In contrast, Tonetti et al. (2012) reported that as 12 months 49 patients (75 adverse events) in the control group and 34 patients (56 adverse events) in the test group. The authors reported no difference in the incidence of adverse events was observed between the groups (a test of significance was not carried out).

3.6 Risk of Bias

FQ-1

All studies were assessed as prospective cohorts (SPC being the exposure) using the modified version of the NOS. Overall, most studies had a low risk of bias (Appendix S12), assessed as having five out of a possible six stars in regard to the selection and outcome domains. Two studies were found to have a moderate risk of bias, with four stars (Hou et al. 1997, Loesche et al. 2002), with one of these studies having a low score in the exposure/ outcome domain (Hou et al. 1997). When assessed by means according to domains of the NOS, it was found that 'selection' had an average score of 2.9 (SD ± 0.3), whilst the 'outcome/ exposure domain' showed an average 2.5 (SD ± 0.6).

FQ-2

Four RCTs were assessed using the Cochrane Risk of Bias Tool 2.0 (Appendix S13). Three studies were judged as being of, 'some concern' (Bogren et al. 2008, Lulic et al. 2009, Tonetti et al. 2012), whilst one study was deemed to be, 'high' risk (Killeen et al. 2018).

The Robins-I tool was used to assess the quality of one interventional non-randomised controlled trial (Jenkins et al. 2000) and one prospective cohort (Costa et al. 2015). Both studies were judged to be of 'serious' overall risk of bias (Appendix S14).

4. DISCUSSION

4.1 Key Findings

Findings of the meta-analyses indicated that the proportion of patients who experienced tooth loss was 9.6% (95% CI 5-14%) i.e. 10% of patients can expect to lose at least one tooth during SPC of at least 5 years duration. Subgroup analysis showed that the proportion of patients with regular 3 monthly SPC recall visits whom experienced tooth loss was 8.0% (95% CI 2-14%), compared with 11.9% (95% CI 5-19%) for the IRREG SPC group (p~~P~~=0.161). A shorter length of follow-up (5-10 years) corresponded to an average of 8.2% (95% CI 3-13%), and as this time period increased (>10 years), the proportion also increased to 12.7% (95% CI 4-22%). Studies which could not be included in the meta-analyses reported a mean tooth loss per patient of 0-2.7 (±3.7), which was not greatly affected by the length of follow-up in SPC.

Patients who experienced at least one site of CAL loss≥2 mm was estimated to be 24.8% (95% CI 11-38%) i.e. 25% of patients can expect to have at least one site with progression of periodontitis by at least 2 mm during SPC of at least 5 years duration. According to the subgroup analyses, more patients who underwent 3 monthly SPC experienced CAL loss≥2 mm, which amounted to 30.2% (95% CI -~~0~~2 – ~~0.6~~63%), whilst the proportion of those in IRREG group SPC was 21.4% (95% CI 10-33%). The longer length of follow up of >10 years, led to a slightly higher proportion of patients with attachment loss of 26.3% (95% CI 8-45%) as compared to 22.1% (95% CI 5-39%) for the 5-10 yr group.

4.2 Agreements and Disagreements with Other Reviews

To our knowledge, this is the first systematic review assessing disease progression with the primary outcome of tooth loss, in the phase of SPC in the long term (> 5years).

The results of our review agree with a recent Cochrane review (Manresa et al. 2018) which reported on RCTs with a minimum of 12 months follow-up to determine the effects of maintenance care in the management of periodontitis. The authors found the quality of evidence to be low or very low and could not make conclusions on the merit of SPC

versus monitoring alone/irregular SPC. Furthermore, no conclusion could be drawn regarding the optimum frequency of SPC.

One recent systematic review (Sanz-Martin et al. 2019) similar to the present review, reported mean CAL loss ranging from ≤0.5 mm to >1 mm and proportion of sites showing CAL loss≥ 2mm ranging from 3-20% in their qualitative review. We were unable to compare the outcomes, as reporting of CAL loss in the current review was different and on a patient level. Tooth loss was reported at 1% based on one study only. One explanation for the differing results could be that Sanz-Martin et al. (2019) excluded regeneration studies, which formed a key part of the current review. Additionally, the present review only included studies with minimum 5 years specifically in the phase of SPC, rather than 5 years follow-up (which was often calculated before APT). Quality assessment also differed. The present review employed the modified version of the NOS to assess the SPC phase only, whereas the previous authors assessed studies based on the APT phase (thereby using the Cochrane collaboration tool for RCT and NOS for prospective cohorts). Their judgement was thus that most studies were at a high risk of bias, compared with this review which found that most studies were at low risk of bias.

4.2.1. Overall completeness and applicability of the evidence

This review intended to focus on patients diagnosed with stage IV periodontitis, however, the majority of studies were published prior to the most recent classification, with the exception of one (Cortellini et al. 2020), whereby the authors retrospectively classified patients as stage III-IV. No data could be extracted on what would specifically be considered stage IV periodontitis. In light of the fact that we have a lack of data on complexity factors such as numbers of teeth previously lost to periodontitis, masticatory dysfunction, bite collapse and/ or remaining teeth, it would be reasonable to assume that the majority of studies in this review probably represent stage III periodontitis patients. It is unclear to what extent complexity factors might influence disease recurrence in SPC, and thus our results might be generalised to include stage IV cases.

The limited number of studies included in this systematic review might seem surprising, however prospective long-term studies (> 5 years) in the periodontal literature are rare, with majority having a clear focus on the outcomes of APT with ≤12 months follow-up.

It is unclear if the data presented are representative of disease occurrence, recurrence or progression, furthermore, it is unclear if tooth loss was due to periodontitis alone. A number of studies did not present any information on reasons for tooth loss, thus the results presented in this review could be over-estimated. Although our subgroup analysis, showed that the proportion of patients who experienced CAL loss≥2 mm was greater for those in the 3M subgroup than the IRREG SPC subgroup, this difference was not statistically significant. Additionally, the disparity may be explained by a single outlier (Cortellini et al. 2017) whereby participants in this group presented with a greater number of residual PPD at the start of SPC and subsequently greater disease recurrence.

The studies in this systematic review were largely conducted in the university setting, with only a few conducted in private practice, some of which were from the same practice. Additionally, the meta-analyses included studies whereby regenerative procedures were part of APT, which limits the applicability of the evidence to all periodontal patients in general practice. The variability of SPC recall intervals and possible variety of operators however, may be more realistic of that which occurs in practice. This systematic review was also unable to inform on specialist versus non-specialist SPC in regard to disease progression/recurrence. A previous systematic review (Gaunt et al. 2008) reported that SPC delivered in specialist care represented a greater financial cost, but this was accompanied by greater periodontal stability (CAL) over a minimum follow-up period of 12 months.

There was an obvious lack of detail in regard to the description of SPC and the majority of studies provided no information on whom carried out the recall appointments. Use of the CONSORT – NPS extension (Leow et al. 2016) might help guide authors to describe the SPC intervention more completely even for non-randomised trials.

Studies which included PRO and health economic data were clearly lacking, therefore no conclusions could be made on the impact of disease recurrence in regard to these important outcomes from this review. However, health economic modelling of SPC has

demonstrated that it is cost-effective in developed economies when considering tooth loss or progression of CAL (Pennington et al. 2011). Furthermore, prevention of tooth loss in an aging population is a priority for long-term health and wellbeing (Tonetti et al. 2017). In relation to oral health-related quality of life (OHQoL) a recent pilot study has shown that after 32 years of SPC, OHQoL impacts are low. Interestingly, there were higher OHQoL impacts associated with 'insufficient' adherence to SPC compared with those with 'sufficient' adherence (Graetz et al. 2020).

Four studies specifically investigated treatment of recurrence in SPC, with only two being RCTs. Due to heterogeneity in terms of methodology and outcome reporting we were unable to answer FQ-2. Some of the included studies that addressed FQ-1 indicated that management of recurrence was left to the discretion of the operators, but usually were managed by further subgingival debridement. Success of this treatment modality in regard to resolution or halting progression of disease was not reported, although one study mentioned that, 'most' recurrent sites responded favourably to NST (Costa et al. 2015).

4.2.2. Overall Quality, Strength, and Consistency of the Evidence

The quality assessment judged the majority of included studies had a low risk of bias in regard to the SPC phase (FQ-1), with two studies found as having moderate risk. The meta-analysis highlighted heterogeneity for both tooth loss and CAL loss≥2 mm, which reflects the limited number of studies fulfilling the inclusion criteria for this systematic review. Type of initial therapy (regenerative or non-regenerative) was one factor that could explain some heterogeneity, however residual unexplained heterogeneity should be assumed, and results should be interpreted with caution. Studies included in the meta-analysis were predominantly of a regenerative nature. Split mouth studies were included in this review, and it should be acknowledged that there is an uncertain risk of contamination from one side/ quadrant to another. This, however, would be most relevant for studies assessing APT. The strength of the evidence to answer FQ-2 was weak, with two studies having a, 'serious' risk of bias (Robins-I tool), three studies of, 'some concern' and one study determined as having a, 'high' risk of bias (Cochrane Risk of Bias Tool 2.0). There was no clarity on which treatment modality (if any) was superior in the management of disease recurrence/ progression in SPC.

Finally, it should be recognised that studies included in this review were not originally designed for assessment of disease progression/recurrence and/or treatment of recurrence in SPC, thus the strength of conclusions from these studies is weak.

4.3 Strengths and Limitations of the Review

In order to minimise the risk of bias in the review process, this protocol was submitted *a priori* to PROSPERO. Furthermore, screening, study eligibility, data abstraction and quality assessment were all conducted in duplicate and independently.

This systematic review is the first to comprehensively look at disease progression/ recurrence in SPC, incorporating all forms of treatment in APT, over a minimum of 5 years in maintenance. Additionally, it is the first to assess methods of managing disease progression/ recurrence of patients in an established SPC programme. We incorporated a sensitive search strategy in multiple electronic databases in order to detect a broad range of studies. Other strengths were the quality assurance including duplicate, independent study screening and data extraction.

A number of studies described a significant number of drop-outs over the follow up period, and in order not to underestimate the prevalence of tooth loss and CAL loss≥2 mm we chose to carry out a per protocol meta-analyses, however for comparison and thoroughness, an ITT analysis was also included for tooth loss.

A number of limitations could be identified which might bias the outcomes of this systematic review.

Publication bias is an important problem in evidence-based Medicine, and this may lead to selection bias in systematic reviews. In the present review, some publications following the screening of titles and abstracts could not be obtained in full-text and clarification on studies from authors could not be followed up. We were also limited to

publications in the English language, which means that relevant studies could have been missed.

Some post-hoc changes were made to the original protocol. We added case-series to the exclusion criteria, and a distinction was also made as to what we defined as a case-series versus prospective cohort. Additionally, a modified version of the NOS needed to be implemented to adjust for the studies included in the review.

One post-hoc analysis was included based on the data collected. This was subgrouping according to SPC recall intervals and was conducted as it became clear that a number of studies had quite variable or unmonitored SPC visits.

4.4 Implications for Practice and Policy

Most patients enrolled in SPC following successful treatment of periodontitis should not expect to experience tooth loss, which, considering the severity of disease (stage III or IV periodontitis) is highly encouraging. However, 25% of patients are likely to experience further CAL loss. It is unclear from the data whether the CAL loss represents periodontitis progression or gingival recession in shallow pockets. However, in some studies (Bogren et al. 2008, Costa et al. 2015, Cortellini et al. 2017), CAL loss was noted as an increase in PPD at some sites, suggesting disease progression. These findings, together with other evidence discussed in this review, highlight that SPC is an important element in the long-term management of stage III and IV periodontitis.

Evidence external to this review indicates that SPC is cost-effective in developed economies (Pennington et al. 2011, Schwendicke et al. 2020) and that prevention of tooth loss is important in ageing populations (Tonetti et al. 2017).

Although SPC is poorly described in the literature, the common elements in studies suggest that it should include repeated; risk assessment, health behaviour motivation, tailored oral hygiene coaching, professional mechanical plaque removal and targeted subgingival debridement appropriate for each patient (Rosling et al. 2001). The recently published 'Clinical Practice Guideline~~s~~' from the recent European Federation of Periodontology (Sanz et al. 2020) supports inclusion of these elements also. Individual

needs of each patient should be considered when deciding on the frequency of SPC, and, until the influence of risk factors is better understood, this is likely to be no longer than 3-6 monthly for stage III-IV periodontitis patients. Whilst there was no evidence of a difference in tooth loss between groups receiving 3 monthly and less regular SPC, it is important to remember that these were not randomised controlled trials and were therefore at higher risk of bias. A lack of randomised evidence was also found in another systematic review (Manresa et al. 2018).

4.5 Implications for Further Research

There is a clear need for high quality trials focussed on SPC, with particular attention to SPC recall intervals, and documenting and treating disease progression/ recurrence. SPC should be carefully described in detail including who delivered it and the components of care using the CONSORT-NPE as a guide, even for non-randomised studies. The demographics of the population entering SPC should be clearly described, particularly with reference to risk factors of smoking and diabetes. Information on tailoring procedures in each SPC visit and recall intervals would be highly valued.

In order to increase the clinical relevance of studies, it would be ideal to report outcomes such as tooth loss or CAL loss at a patient level, in addition to mean values. Patient reported outcomes and costs of treatment would also be important and essential aspects of a clinical trial.

5. CONCLUSIONS

Within the limitations of this study, we have found that the mean prevalence of tooth loss in patients in SPC for 5 years or more is less than 10% of patients, with a tendency for greater prevalence with time. Regular SPC appointments (3 monthly) appears to be important for reduction of the prevalence of tooth loss.

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Figure 1. Flow diagram of the systematic review

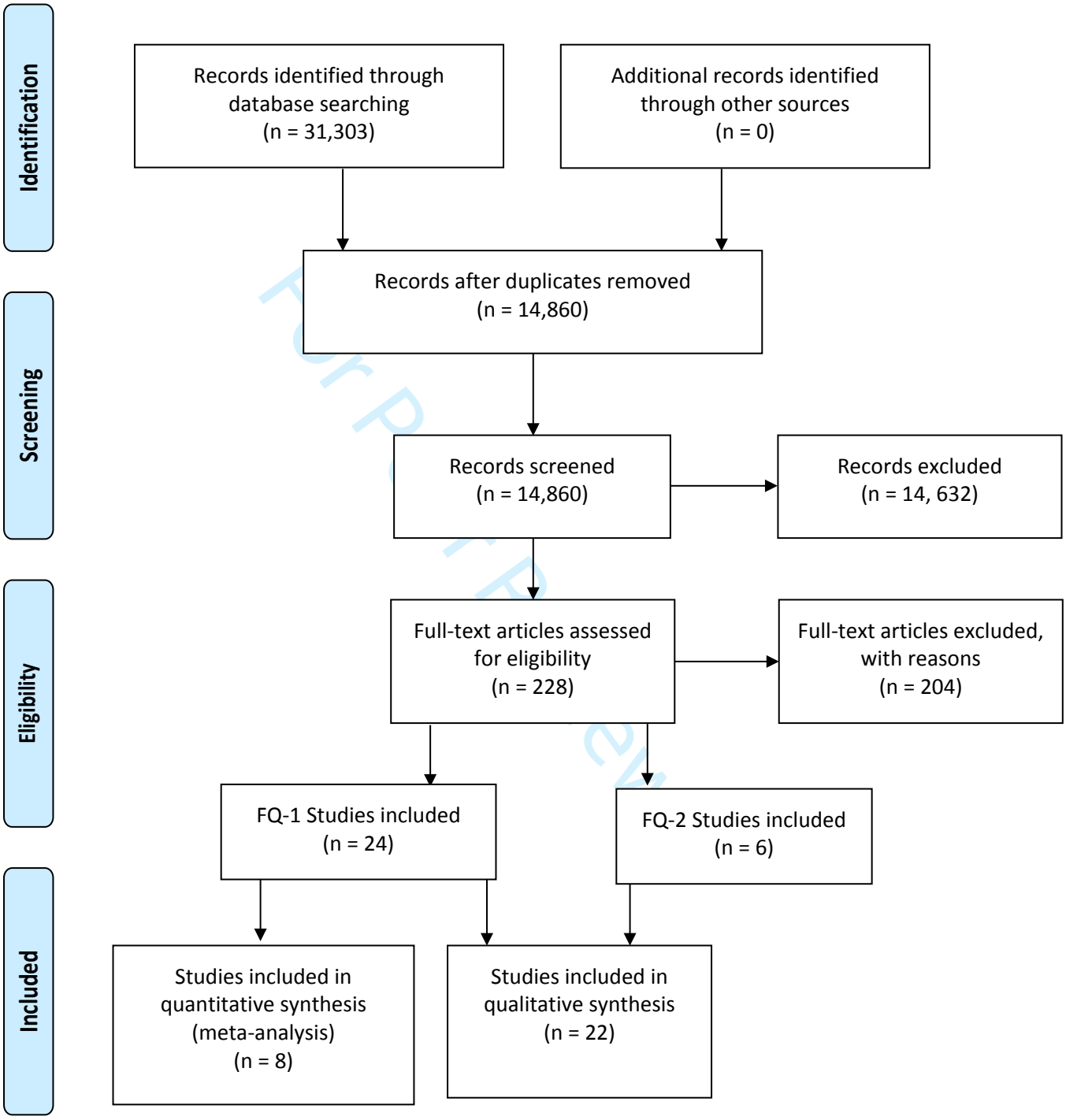
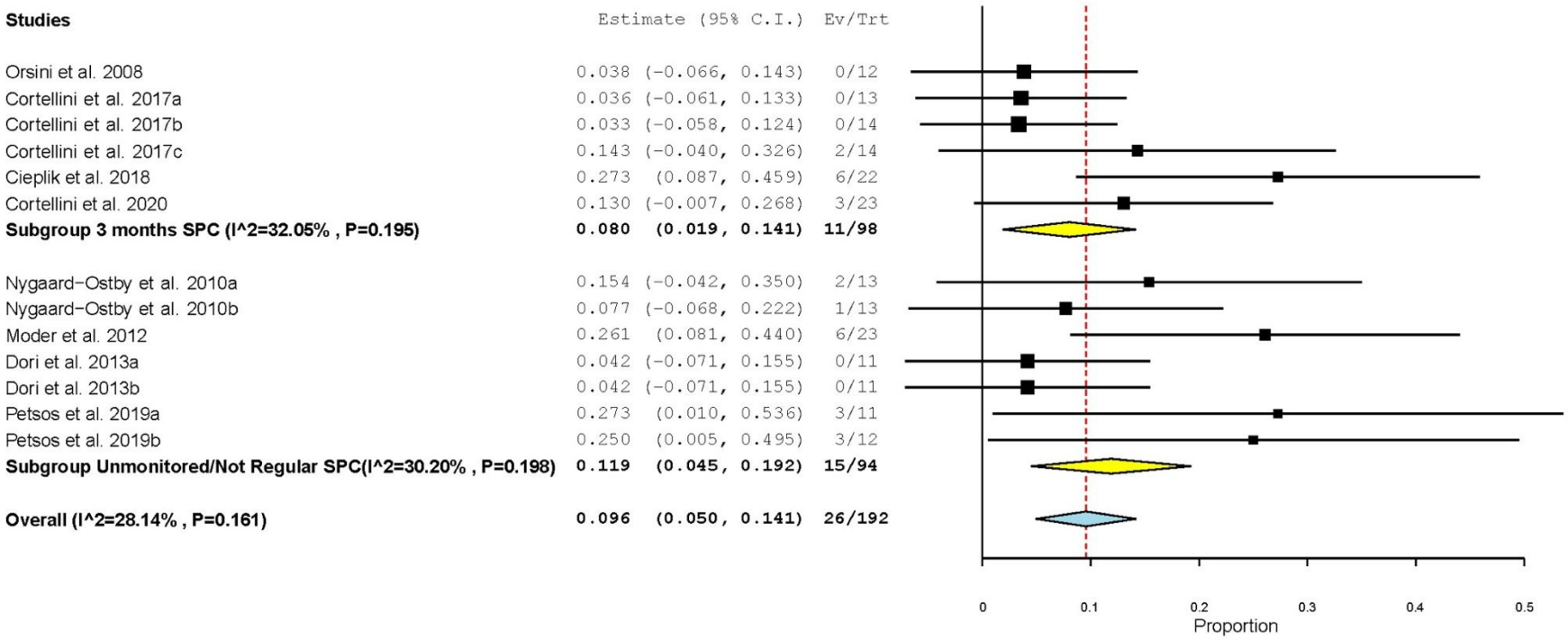
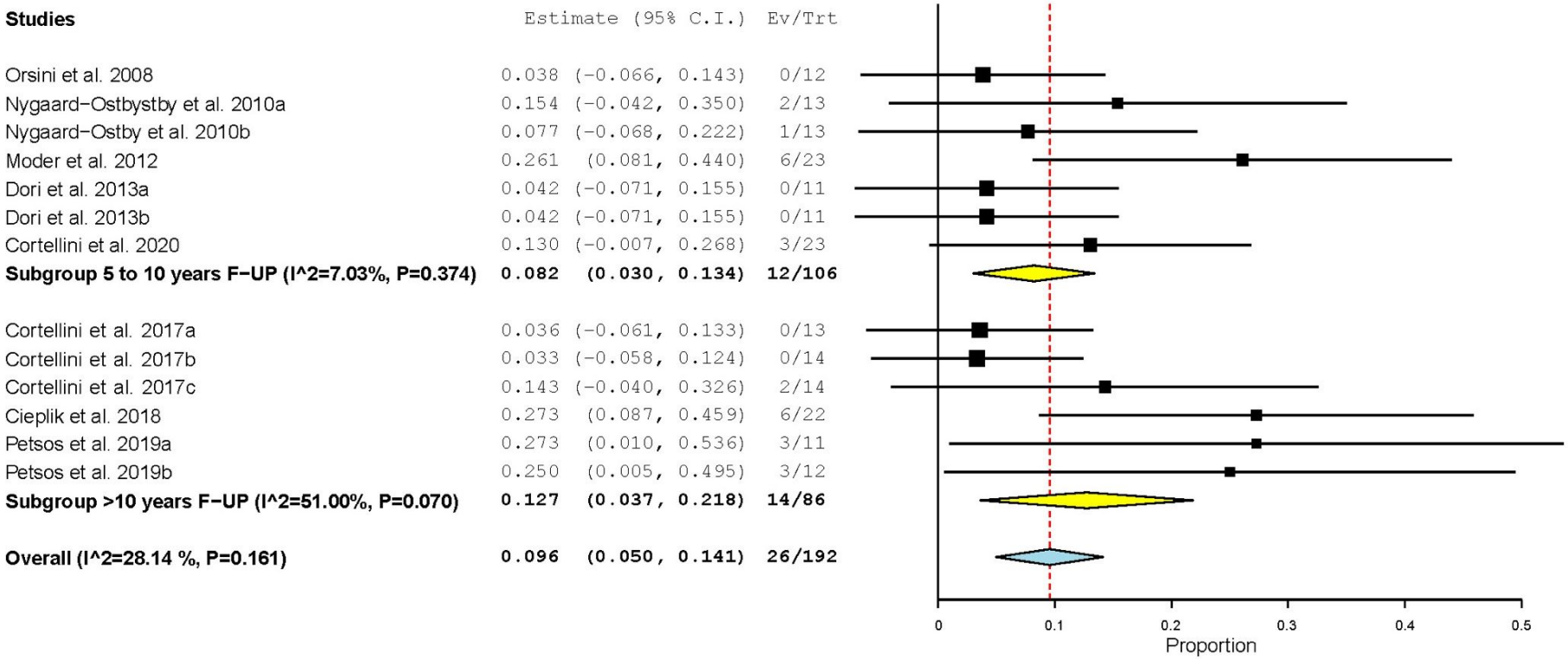


Figure 2. Forest plot of the proportion of patients who experienced tooth loss according to frequency of ~~SPC~~ supportive periodontal care (SPC) - ~~(~~per protocol~~)~~.



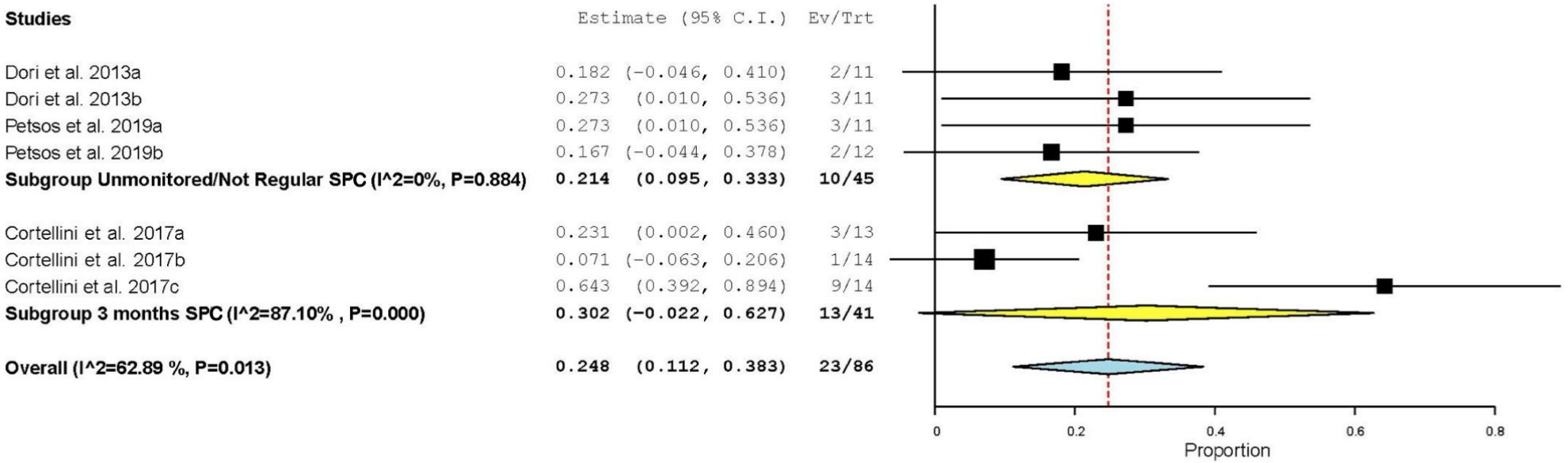
F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Figure 3. Forest plot of the proportion of patients who experienced tooth loss according to length of follow up (per protocol).



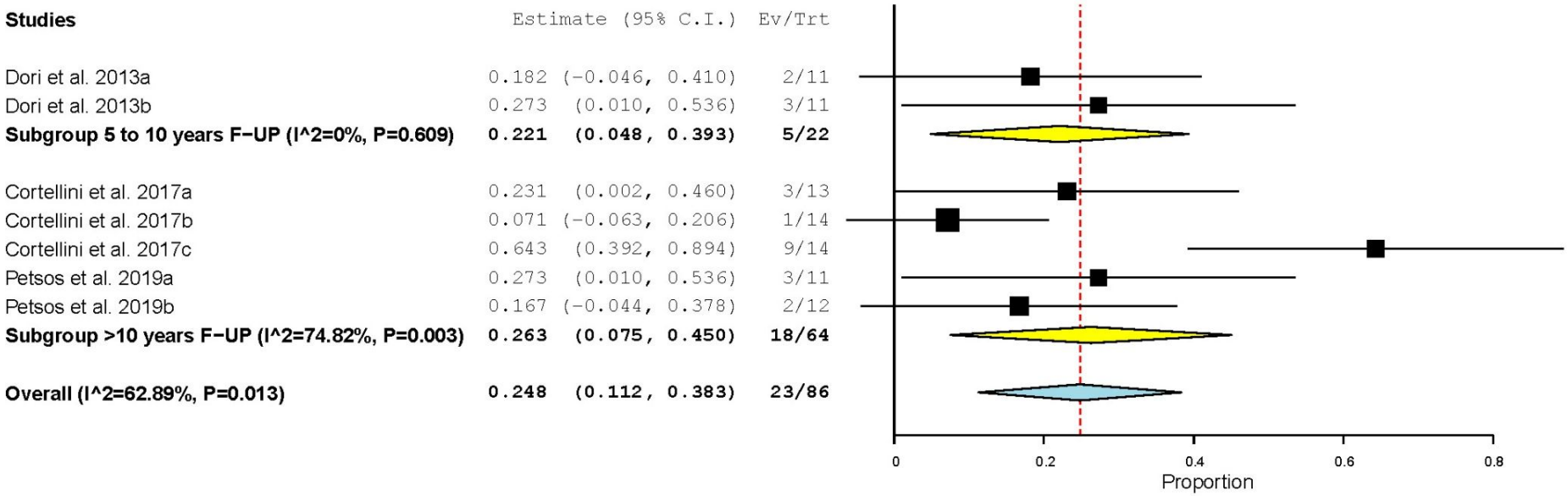
F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Figure 4. Forest plot of proportion of patients with at least one site of clinical attachment loss ≥2 mm according to frequency of supportive periodontal care (SPC) - per protocol.



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Figure 5. Forest plot of the proportion of patients with at least one site of clinical attachment loss ≥2 mm at patient level according to length of follow-up (per protocol).



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Table 1. Focussed Question -1: Characteristics of included studies

Publication	Country	Setting	Funding	Diagnosis	APT
Axelsson & Lindhe 1981	Sweden	University	NR	Adv. periodontal disease	Surgery: MWF in all four quadrants
Becker et al. 2001	USA	University	NR	Mod-Adv. adult periodontitis	Split mouth (RCT) a; SRP with LA b; Surgery: osseous recontouring c; Surgery: MWF
Buchmann et al. 2002	Germany	University	NR	Aggressive periodontitis	Surgery: MWF in all four quadrants
Cieplik et al. 2018	Germany	University	Partly supported by Robert Matheys Foundation (Bettlack Switzerland)	Aggressive / chronic periodontitis	Split mouth (RCT) a; GTR + ß-TCP granules (soaked in blood) b; GTR + ß-TCP granules (soaked in APC)
Cortellini et al. 2017	Italy	Private Practice	Partly supported by Accademia Tosacana di	NR (angular defects)	RCT a; Surgery: MWF

			Ricerca Odontostomatologica, Italy European Research Group on Periodontology, Genova, Italy		b; Surgery: MPPT with e-PTFE c; Surgery: Flap with e-PTFE
Cortellini et al. 2020	Italy	Private Practice	Partly supported by the European Research Group on Periodontology (ERGOPerio), Berne, Switzerland	Stage III/IV periodontitis (generalised)	RCT (only one arm assessed for this review) Surgery: PPF (Membrane or EMD/ Membrane+xenograft/ EMD+alloplast or EMD+membrane)
Crespi et al. 2011	Italy	Private Practice	NR	Mod-Adv. adult periodontitis	Split mouth a; Surgery: MWF (quadrant) b; Surgery: CAF + CO_2 laser root conditioning
Dori et al. 2013	Hungary	University	NR	Adv. chronic periodontitis	RCT a; Surgery: EMD + xenograft

					b; Surgery: EMD+ ß-TCP granules
Hou et al. 1997	Taiwan	University	NR	Mod-Adv. adult periodontitis	SRP with LA
Kaldahl et al. 1996a	USA	University	NIH-NIDR grant DE06103	Mod-Adv. adult periodontitis	Split mouth (RCT) a; coronal scaling b; SRP with LA c; Surgery: MWF d; Surgery: osseous recontouring
Kaldahl et al. 1996b	USA	University	NIH-NIDR grant DE06103	Mod-Adv. adult periodontitis	As above (same population)
Knowles et al. 1979	USA	University	Partly supported by US Public Health Service Grant DE 02731	Mod-Adv. adult periodontitis	Split mouth (RCT), half mouth a; Surgery; Pocket elimination, curettage b; Surgery: MWF, curettage c; Surgery; MWF, pocket elimination

Loesche et al. 2002	USA	University	US Public Health Service Grant DE-06030 from the National institute of Dental and Craniofacial Research	Adv. periodontal disease (chronic/ adult/ aggressive/ early onset)	RCT a; NST + placebo (systemic) b; NST + Metronidazole (systemic) c; NST + Doxycycline (systemic)
Loesche et al. 2005	USA	University	US Public Health Service Grant DE-06030 from the National institute of Dental and Craniofacial Research	Adv. periodontal disease (chronic/ adult/ aggressive/ early onset)	As above (same population)
Moder et al. 2012	Germany	University	Robert Matheys Stiftung (RMS Foundation, Bettlach, CH)	Aggressive/chronic periodontitis	Split mouth (RCT) a; GTR + ß-TCP granules (soaked in blood) b; GTR + ß-TCP granules (soaked in APC)
Nygaard-Ostby et al. 2010	Norway	Private Practice	Supported by grant from Atrix	Chronic periodontitis (+ angular defect)	RCT

			Laborators Inc., Fort Collins, CO, USA		a; Surgery: Autogenous bone graft b; Surgery: Autogenous bone graft + GTR
Orsini et al. 2008	Italy	Unclear	National Research Council (CNR), Finalized Project Materials Tailored for Advanced Technologies PF MSTA II, Ministry of University, Research, Science and Technology (MURST) Italy	NR (angular defect)	Split mouth (RCT) a: Surgery: Autogenous bone graft + resorbable membrane b: Surgery: Autogenous bone graft + calcium sulphate graft
Petsos et al. 2019	Germany	University	Partly by Moessner Stiftung research grant (Frankfurt am Main, Germany) to the Centre for	Severe chronic periodontitis (+ angular defect)	RCT a: Surgery: OFD b: Surgery: OFD + resorbable membrane

			Dentistry and Oral Medicine (Carolinum)		
Pihlstrom et al. 1983	USA	University	NR	Mod-Adv. adult periodontitis	Split mouth (RCT) a: SRP with LA b: Surgery: MWF
Pihlstrom 1984	USA	University	NR	Mod-Adv. adult periodontitis	As above (same population)
Ramberg et al. 2001	Sweden	University	Grants from NIDCR (DE-12861) and Colgate Technology Centre, NJ USA	Adv. periodontitis	a: SRP b: SRP + Tetracycline (systemic)
Rosling et al. 2001	Sweden	University and 12 Community Dental Clinics	Supported by grants from NIDCR (DE-12861) and Colgate Technology Centre, NJ, USA	Adv. periodontitis or normal prevalence of periodontal disease	NST

Serino et al. 2001a	Sweden	University	Colgate Technology Centre, NJ, USA and NIDCR (DE-12861) Bethesda, Maryland USA	Adv. periodontal disease	NST + Metronidazole (systemic) + Amoxycillin (systemic)
Serino 2001b	Sweden	University	NIDCR (DE-12861) and Colgate Technology Centre, NJ, USA	Adv. periodontal disease	RCT a: SRP b: Surgery: MWF

NR: Not reported Adv.: advanced, Mod-Adv.: moderate to advanced, MWF: Modified Widman Flap, RCT: randomised controlled trial, SRP: scaling and root planing, NST: non-surgical therapy, LA: local anaesthetic, GTR: guided tissue regeneration, ß-TCP: Beta tricalcium phosphate, APC: ~~autogeneous~~autogenous platelet concentrate, MPPT: modified papilla preservation technique, e-PTFE: expanded-polytetrafluroethylene membrane, EMD: enamel matrix derivative, PPF: papilla preservation flaps, CAF: coronally advanced flap, CO_2: carbon dioxide, OFD: open flap debridement

Table 2. Focussed Question -1: Characteristics of study which are related to supportive periodontal care (SPC)

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
Axelsson & Lindhe 1981	77	0-2yrs – 2m 3-6yrs – 3m	72	- Oral hygiene reviewed. Bass method of brushing, floss, toothpicks advocated. - Supra- and subgingival scaling as required.	Tooth loss (mean) CAL loss (%) PPD (mean) FMBS
Becker et al. 2001	16	0-5yrs – 3m	60	- Oral hygiene reviewed - SRP (1hr) & polish with fluoride paste.	Tooth loss CAL (mean, %) PPD (mean) GI (mean)
Buchmann et al. 2002	13	0-5yrs – 3-6m	60	-Oral hygiene reviewed - Subgingival instrumentation if PPD>4 mm +BOP	CAL (mean, no. of sites) PPD (mean) BOP (%) GI (mean)
Cieplik et al.	22	3m	144	Not reported	Tooth loss

2018					CAL (median) PPD (median)
Cortellini et al. 2017	45	3m	240	-Oral hygiene reviewed -Increased PPD≥2 mm (BOP) and CAL loss≥2 mm, adjunctive periodontal therapy consisting of non-surgical root planing, flap surgery or regenerative surgery as indicated.	Tooth loss CAL (mean) PPD (mean) FMBS (%) Sites requiring re-tx Health economics
Cortellini et al. 2020	25	3m	108	Not reported	Tooth loss CAL (mean) PPD (mean) OHIP Health economics Other PROs
Crespi et al. 2011	25	6m	114	-Oral hygiene reviewed -coronal scaling, polishing & subgingival instrumentation as needed	PPD (mean) GI
				-Occlusal adjustment as	CAL (mean)

Dori et al. 2013	22	3-6m	108	needed -Oral hygiene reviewed -supra- and subgingival scaling and polishing (tailored)	PPD (mean) BOP (per tooth)
Hou et al. 1997	51	1-3m	66	-Oral hygiene reviewed -Repeated instruments where required	CAL (mean) PPD (mean) GI
Kaldahl et al. 1996a	82	3m	84	-Sites ≥3 mm CAL loss received SRP	Tooth loss CAL (mean) PPD (mean) FMBS Other PROs
Kaldahl et al. 1996b	82	3m	84	-Oral hygiene reviewed -Supra- and subgingival instrumentation as needed	CAL (yearly incidence %)
Knowles et al. 1979	78	3m	96	Not reported	CAL (mean)
				- Oral hygiene reviewed. Bass	Tooth loss (range per

Loesche et al. 2002	90	3m	61.2 (median)	method of brushing, floss, toothpicks advocated. - Full mouth instrumentation - Recurrent sites – 1 week of unsupervised systemic metronidazole or placebo	patient and total number) Patients requiring surgery (mean per patient)
Loesche et al. 2005	90	3m	76.8 (median)	- Oral hygiene reviewed. Bass method of brushing, floss, toothpicks advocated. - Full mouth instrumentation - Recurrent sites – 1 week of unsupervised systemic metronidazole or placebo	Pts requiring surgery (mean per patient)
Moder et al. 2012	25	0-1yr – 3m (Univ.) 2-7yrs – 1) 6m (Univ.) or 2) private practice (not recorded)	72	Not reported	Tooth loss CAL (median) PPD (median) PBI
				-Oral hygiene reviewed	Tooth loss

Nygaard-Ostby et al. 2010	40	3,4 or 6m	111	-SRP and polished as needed. Fluoride application and pts advised to use daily 0.05% NaF mouth-rinse	CAL (mean) PPD (mean) PBI
Orsini et al. 2008	12	3m	66	-Oral hygiene reviewed -Instrumentation as needed	Tooth Loss CAL (mean) PPD (mean) FMBS
Petsos et al. 2019	14	Unmonitored	228	Not reported	Tooth Loss CAL (mean) PPD (mean) GBI
Pihlstrom et al. 1983	17	3-4m	72	-Oral hygiene reviewed -Supra- and subgingival instrumentation	CAL (mean) PPD (mean)
Pihlstrom et al. 1984	17	3-4m	72	-Oral hygiene reviewed -Supra- and subgingival instrumentation	Tooth loss CAL (mean) PPD (mean)
				-Oral hygiene reviewed	Tooth loss (mean)

Ramberg et al. 2001	115 (34 periodontitis patients)	3-4m	144	-Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic	CAL PPD (mean) FMBS
Rosling et al. 2001	334 (Highly susceptible group, HSG – 109/ Normal group, NG – 225)	3-4m (HSG) 6-12m (NG)	156	HSG: -Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) Sites with increase of PPD ≥2 mm (%) No. of pts with increase of CAL≥2 mm
Serino et al. 2001a	20	3-4m	60	-Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) PPD (mean) FMBS

Serino et al. 2001b	64	3-4m	144	-Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) PPD (mean) FMBS

yrs: years, CAL: clinical attachment level, PPD: periodontal probing pocket depth, FMBS: full mouth bleeding score, GI: gingival index, SRP: scaling and root planing, BOP: bleeding on probing, re-tx: re-treatment, OHIP: oral health impact profile questionnaire, PRO: patient reported outcomes, Univ.: university setting, PBI: papillary bleeding index, NaF: Sodium fluoride, GBI: gingival bleeding index

Table 3. Focussed Question -2: Characteristics of Included Studies

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
Bogren et al. 2008	Multi-centre (Sweden, USA)	Specialist Private Practice & University	Part funded by National Institute of Dental and Craniofacial Research (Bethesda, Maryland)	- Moderate-advanced periodontitis - Minimum of 4 teeth with PPD≥5 mm	RCT	**Test:** Instrumentation + 8.8% doxycycline gel in PPD≥5 mm at BL, 1 and 2 years. **Control:** Instrumentation alone (PPD≥5 mm)
Costa et al. 2015	Brazil	Private Practice	Grants from Minas Gerais State Foundation & National Counsel of Technological and Scientific Development	- Moderate-advanced chronic periodontitis - Minimum 4 sites with PPD≥5 mm and CAL≥3 mm, BOP and/ suppuration	Prospective Cohort	**RC:** 96 subjects, **IC:** 116 subjects Instrumentation (NST or ST, when appropriate). ST when PPD≥5 mm +

						BOP (45-60 days after NST). Compared treatment of recurrence via NST or ST in RC and IC groups.
Jenkins et al. 2000	UK	University	NR	NR - Minimum of 4 sites with PPD≥4 mm and persistent BOP	CCT	**Test:** Subgingival scaling at 3, 6 and 9 months **Control:** Coronal scaling only (and for any sites with CAL≥2 mm, but excluded from analysis), at 3, 6 and 9 months
Killeen et al. 2018	USA	University	- Dr D. H. Reinhardt Scholar Program - Dr. Mick Dragoo and wife Mary and the Nebraska	- One posterior interproximal PPD≥5 mm with history of BOP	RCT	**Test:** NST + 1mg of Minocycline microspheres (local application) at 0, 6, 12 and 18 months **Control:** NST alone

			Dental Association Foundation			
Lulic et al. 2009	Switzerland	University	Part supported by HEL-Bos Photodynamic Systems GmbH, Austria and by the Clinical Research Foundation (CRF) for the Promotion of Oral Health, Switzerland	- Single PPD≥5 mm with/out concomitant BOP	RCT	**Test:** NST + photosensitizer dye (phenothiazine chloride) + PDT (diode laser, wavelength 670nm and power density 75mW/cm^2) **Control:** NST + photosensitizer dye (phenothiazine chloride)
Tonetti et al. 2012	Multi-centre (Italy, Germany, Greece, Netherlands, Switzerland)	Private Practice & University	European Research Group on Periodontology (ERGOPerio) with an unrestricted grant from IVOCLAR	- Moderate-severed periodontitis - Minimum 4 teeth with residual PPD≥5mm and BOP	RCT	**Test:** Instrumentation + 14% doxycycline gel in PPD≥4 mm at BL. **Control:** Instrumentation alone (PPD≥4 mm)

					Vivadent (Liechtenstein). Doxycycline gel provided by IVOCLAR.

RCT: randomised controlled trial, PPD: periodontal probing pocket depth, CAL: clinical attachment level, BL: baseline, BOP: bleeding on probing, NR: not reported, CCT: controlled clinical trial, RC: regular compliers, IC: irregular compliers, NST: non-surgical therapy, ST: surgical therapy, mg: milligram, PDT: photodynamic therapy, nm: nanometres, mW/cm^2: milliwatt per square centimetre

Table 4. Focussed Question -2: Characteristics of studies related to intervention(s)

Publication	Participants (n)	Recall intervals (months)	Follow Up (months)	Description	Outcomes
Bogren et al. 2008	BL= 128 F= 124	6	36	Parallel group, multicentre (2x private practices, 1x university), RCT Moderate/advanced periodontitis **Test:** NST + 8.8% doxycycline gel in PPD≥5 mm at BL, 1 and 2 years. **Control:** NST alone (PPD≥5 mm)	Tooth loss (mean) CAL (mean) PPD (mean) BOP (mean) No. sites PPD≥5 mm (mean)
Costa et al. 2015	BL= 212 F= 212	Regular: ≤6 Irregular: ≤18	60	Prospective cohort, private practice Moderate/advanced periodontitis **RC:** 96 subjects, **IC:** 116 subjects Instrumentation (NST or ST, when appropriate). ST when PPD≥5 mm + BOP (45-60 days after NST).	Tooth loss (mean) Sites experiencing CAL loss≥2 mm PPD (mean % affected sites) CAL (mean) BOP (mean)

				Compared treatment of recurrence via NST or ST in RC and IC groups.	
Jenkins et al. 2000	BL= 39 F= 31	3	12	Controlled clinical trial Severity of periodontitis – not reported **Test:** Subgingival scaling at 3, 6 and 9 months **Control:** Coronal scaling only (and for any sites with CAL≥2 mm, but excluded from analysis), at 3, 6 and 9 months	No. sites CAL loss ≥2 mm CAL (mean) PPD (mean) BOP (mean)
Killeen et al. 2018	BL= 60 F= 48	6	24	Parallel group, RCT Moderate-severe periodontitis **Test:** NST + 1mg Minocycline microspheres, applied every 6months (4 doses) **Control:** NST alone	PPD (mean) CAL (mean)

Lulic et al. 2009	BL= 10 F= 10	Unclear	12	Parallel group, RCT Chronic periodontitis **Test:** NST+ photosensitizer dye + PDT **Control:** NST + photosensitizer dye	PPD (mean) CAL (mean) BOP (mean)
Tonetti et al. 2012	BL= 202 F= 181	3	12	Parallel group, multicentre, RCT Moderate-severe periodontitis **Test:** NST + 14% doxycycline gel in PPD≥4 mm at BL **Control:** NST alone (PPD≥4 mm)	PPD (mean) CAL (mean) BOP (mean) No. sites PPD≥5 mm (mean) No. sites CAL loss≥2 mm Adverse events

BL: baseline, F: final, CAL: clinical attachment level, PPD: periodontal probing pocket depths, BOP: bleeding on probing, No.: number, RC: regular compliers, IC: irregular compliers, NST: non-surgical therapy, ST: surgical therapy, RCT: randomised controlled trial, PDT: photodynamic therapy

Appendix S1. Search strategy on Ovid Medline

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily from 1946 to 01 May 2020

1	periodontitis/ or aggressive periodontitis/ or chronic periodontitis/ or periodontal abscess/ or periodontal pocket/
2	Periodontal Attachment Loss/
3	Alveolar Bone Loss/
4	periodontit*.tw.
5	periodont* attachment loss.tw
6	(periodontal adj2 pocket*).tw.
7	(bleeding adj3 (probing or probe*)).tw.
8	(alveolar adj2 (loss* or atroph*)).tw.
9	((periodont* or alveolar) adj resorption*).tw.
10	or/1-9
11	supportive periodontal therap*.tw.
12	supportive periodontal care.tw.
13	SPT.tw.
14	((periodont* or dentition or dental or tooth or teeth) adj4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)).tw.
15	(recall maintenance or maintenance therap*).tw
16	preventive maintenance.tw.
17	((post surg* or postsurgic*) adj recall).tw.
18	Secondary prevention/
19	Preventive dentistry/
20	exp Dental prophylaxis/
21	dental prophylaxis.tw.
22	oral prophylaxis.tw.
23	(root adj (plane* or planing)).tw.
24	((Dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) adj6 (scaling or scaler* or curettage or curette*)).tw.
25	((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) adj debridement*).tw.

26	Subgingival curettage/
27	exp Diagnosis, Oral/
28	((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos?s)).tw.
29	((dental or oral or teeth or tooth or proximal surface*) adj3 (radiograph* or ex-ray or xray or ex-rays or x-rays)).tw.
30	Radiography, Dental/
31	exp Oral hygiene/
32	oral hygiene.mp.
33	(mouth adj3 hygiene).tw.
34	(mouth adj3 care).tw.
35	(dental adj3 care).tw.
36	(care adj3 teeth).tw
37	(oral adj3 care).tw.
38	plaque control*.tw.
39	(professional adj2 plaque* removal).tw.
40	PMPR.tw.
41	Health Education, Dental/
42	((health adj5 promot*) and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
43	(health awar* and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
44	((Dental or teeth or mouth or periodont* or gingival or oral) and (instruct* or advis* or advic* or educat* or teach* or train*)).tw.
45	Dental care/
46	Comprehensive Dental care/
47	exp animals/ not humans.sh.
48	or/11-46
49	10 and 48
50	49 not 47
51	limit 50 to english language

Appendix S2. Search strategy on Ovid EMBASE Classic and EMBASE

OVID Embase Classic+Embase from 1947 to 01 May 2020

1	periodontitis/ or aggressive periodontitis/ or chronic periodontitis/ or periodontal abscess/ or periodontal pocket/
2	alveolar bone loss/
3	periodontit*.tw.
4	periodont* attachment loss.tw.
5	(periodontal adj2 pocket*).tw.
6	(bleeding adj3 (probe* or probing)).tw.
7	(alveolar adj2 (loss* or atroph*)).tw.
8	((periodont* or alveolar) adj resorption*).tw.
9	or/1-8
10	supportive periodontal therap*.tw.
11	supportive periodontal care.tw.
12	SPT.tw.
13	((periodont* or dentition or dental or tooth or teeth) adj4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)).tw
14	recall maintenance.tw.
15	(preventive maintenance or maintenance therap*).tw.
16	((post surg* or postsurgic*) adj recall).tw.
17	secondary prevention/
18	preventive dentistry/
19	exp dental prophylaxis/
20	dental prophylaxis.tw.
21	oral prophylaxis.tw.
22	((Dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) adj6 (scaling or scaler* or curettage or curette*)).tw.
23	((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) adj debridement*).tw.
24	(root adj (plane* or planing)).tw.
25	dental curettage/ or periodontal procedure/
26	dental health education/

27	((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos?s)).tw.
28	tooth radiography/
29	((dental or oral or teeth or tooth or proximal surface*) adj3 (radiograph* or ex-ray or xray or ex-rays or x-rays)).tw
30	mouth hygiene/
31	oral hygiene.tw.
32	(mouth adj3 hygiene).tw
33	(mouth adj3 care).tw.
34	(dental adj3 care).tw.
35	(care adj3 teeth).tw
36	(oral adj3 care).tw.
37	plaque control*.tw.
38	(professional adj2 plaque* removal).tw.
39	PMPR.tw.
40	((health adj5 promot*) and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
41	(health awar* and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
42	((Dental or teeth or mouth or periodont* or gingival or oral) and (instruct* or advis* or advic* or educat* or teach* or train*)).tw.
43	dental prevention/
44	or/10-43
45	9 and 44
46	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
47	45 not 46
48	limit 47 to english language

Appendix S3. Search strategy on LILACS VHL Regional Portal

LILACS VHL Regional Portal (date run 02 May 2020)

tw:((tw:(periodontit* OR "bleeding on probing" OR "bleeding upon probing" OR "alveolar bone loss")) AND (tw:("supportive periodontal therapy" OR "supportive periodontal care" OR "dental prophylaxis" OR "oral prophylaxis" OR "root planing" OR "oral hygiene" OR "mouth care" OR "mouth hygiene" OR "dental care" OR "dental hygiene" OR "oral care" OR "plaque removal" OR "plaque control" OR debridement* OR scaling OR scaler* OR curettage OR radiograph* OR "ex-ray" OR xray OR "ex-rays" OR "x-rays" OR "health promotion" OR check-up* OR checkup* OR "check up" OR "check ups" OR examination* OR recall* OR visit* OR diagnos* OR maintenance OR maintain* OR posttreat* OR post-treat* OR prevent*)) NOT (tw:((mh:animals OR mh:rabbits OR mh:rats OR mh:primates OR mh:dogs OR mh:cats OR mh:swine OR pt:"in vitro")))) AND (db:("LILACS") AND la:("en"))

Appendix S4. Search strategy on Cochrane Centre Register of Controlled Trials

Cochrane Central Register of Controlled Trials (CENTRAL) (date run 02 May 2020)

#1	MeSH descriptor: [Periodontitis] this term only
#2	MeSH descriptor: [Aggressive Periodontitis] this term only
#3	MeSH descriptor: [Chronic Periodontitis] this term only
#4	MeSH descriptor: [Periodontal Abscess] this term only
#5	MeSH descriptor: [Periodontal Pocket] this term only
#6	MeSH descriptor: [Periodontal Attachment Loss] this term only
#7	MeSH descriptor: [Alveolar Bone Loss] this term only
#8	(periodontit*):ti,ab,kw
#9	(periodont* NEAR/1 "attachment loss"):ti,ab,kw
#10	(periodontal NEAR/1 pocket*):ti,ab,kw
#11	(("bleeding on probing" OR "bleeding upon probing")):ti,ab,kw
#12	(alveolar NEAR/1 (loss* or atroph*)):ti,ab,kw
#13	((periodont* or alveolar) NEAR/2 resorption*):ti,ab,kw
#14	(Tsakos et al. -#13)
#15	(supportive periodontal therap*):ti,ab,kw
#16	(supportive periodontal care):ti,ab,kw
#17	(SPT):ti,ab,kw
#18	((periodont* OR dentition OR dental OR tooth OR teeth) NEAR/3 (maintain* OR maintenance OR posttreat* OR post-treat* OR "post treat*" OR prevent*)):ti,ab,kw
#19	("recall maintenance"):ti,ab,kw
#20	("preventive maintenance"):ti,ab,kw
#21	((post-surg* OR postsurgic* OR "post surg*") NEXT recall):ti,ab,kw
#22	MeSH descriptor: [Secondary Prevention] this term only
#23	MeSH descriptor: [Preventive Dentistry] this term only
#24	MeSH descriptor: [Dental Prophylaxis] explode all trees
#25	("dental prophylaxis"):ti,ab,kw
#26	("oral prophylaxis"):ti,ab,kw
#27	(root NEXT (plane* or planing)):ti,ab,kw
#28	MeSH descriptor: [Dental Devices, Home Care] this term only

#29	((Dental OR oral OR teeth OR tooth OR supragingival OR supra-gingival OR "supra gingival" OR subgingival OR sub-gingival OR "sub gingival") NEAR/5 (scaling or scaler* or curettage or curette*)):ti,ab,kw
#30	((periodontal OR supra-gingival OR supragingival OR sub-gingival OR subgingival OR "supra gingival" OR "sub gingival") NEXT debridement*):ti,ab,kw
#31	MeSH descriptor: [Subgingival Curettage] explode all trees
#32	MeSH descriptor: [Diagnosis, Oral] explode all trees
#33	(((intraoral OR intra-oral OR "intra oral" OR extraoral OR extra-oral OR "extra oral") NEAR/3 (check-up* OR checkup* OR "check up*" OR inspect* OR exam* OR attend* OR recall* OR visit* OR diagnos?s))):ti,ab,kw
#34	((dental OR oral OR teeth OR tooth OR "proximal surface*") NEAR/2 (radiograph* OR ex-ray OR xray OR ex-rays OR x-rays OR "x ray*" OR "ex ray*")):ti,ab,kw
#35	MeSH descriptor: [Oral Hygiene] explode all trees
#36	("oral hygiene"):ti,ab,kw
#37	(mouth NEAR/2 hygiene):ti,ab,kw
#38	(mouth NEAR/2 care):ti,ab,kw
#39	(dental NEAR/2 care):ti,ab,kw
#40	(care NEAR/2 teeth):ti,ab,kw
#41	(oral NEAR/2 care):ti,ab,kw
#42	("plaque control*"):ti,ab,kw
#43	(professional NEAR/1 "plaque* removal"):ti,ab,kw
#44	(PMPR):ti,ab,kw
#45	(((health NEAR/4 promot*) AND (dental OR teeth OR mouth OR periodont* OR gingiv* OR oral))):ti,ab,kw
#46	((health NEAR/3 awar*) AND (dental OR teeth OR mouth OR periodont* OR gingiv* OR oral)):ti,ab,kw
#47	((dental OR teeth OR mouth OR periodont* OR gingival OR oral) AND (instruct* OR advis* OR advic* OR educat* OR teach* OR train*)):ti,ab,kw
#48	MeSH descriptor: [Dental Care] this term only
#49	MeSH descriptor: [Comprehensive Health Care] this term only
#50	{OR #15-#49}
#51	#14 AND #50 in Trials

Appendix S5. Search strategy on Dentistry and Oral Science Source EBSCOHost

Dentistry and Oral Science Source EBSCOHost (date run 02 May 2020)

S1	TI periodontit* OR AB periodontit*
S2	TI "periodont* attachment loss" OR AB "periodont* attachment loss"
S3	TI periodontal N1 pocket* OR AB periodontal N1 pocket*
S4	TI ((bleed*) N3 (probe* OR probing)) OR AB ((bleed*) N3 (probe* OR probing))
S5	TI (alveolar N2 (loss* or atroph*)) OR AB (alveolar N2 (loss* or atroph*))
S6	TI ((periodont* or alveolar) N1 resorption*) OR AB ((periodont* or alveolar) N1 resorption*)
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	TI "supportive periodontal therap*" OR AB "supportive periodontal therap*"
S9	TI "supportive periodontal care" OR AB "supportive periodontal care"
S10	TI SPT OR AB SPT
S11	TI (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*) OR AB (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)
S12	TI "recall maintenance*" OR AB "recall maintenance*"
S13	TI "preventive maintenance" OR AB "preventive maintenance"
S14	TI ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall) OR AB ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall)
S15	TI "dental prophylaxis" OR AB "dental prophylaxis"
S16	TI "oral prophylaxis" OR AB "oral prophylaxis"
S17	TI (root W0 (plane* or planing)) OR AB (root W0 (plane* or planing))
S18	TI ((dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) N7 (scaling or scaler* or curettage or curette*)) OR AB ((dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) N7 (scaling or scaler* or curettage or curette*))
S19	TI ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*) OR AB ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*)

S20	TI ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s)) OR AB ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s))
S21	TI ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or x-ray or "ex rays")) OR AB ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or x-ray or "ex rays"))
S22	TI "oral hygiene" OR AB "oral hygiene"
S23	TI mouth N2 hygiene OR AB mouth N2 hygiene
S24	TI mouth N3 care OR AB mouth N3 care
S25	TI dental N3 care OR AB dental N3 care
S26	TI care N3 teeth OR AB care N3 teeth
S27	TI oral N3 care AND AB oral N3 care
S28	TI "plaque control*" OR AB "plaque control*"
S29	TI professional N2 "plaque* removal" OR AB professional N2 "plaque* removal"
S30	TI PMPR OR AB PMPR
S31	TI (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S32	TI ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S33	TI ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*)) OR AB ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*))
S34	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S35	S7 AND S34
S36	TI (rats or rat or animal or animals or mice or mouse or "in vitro") OR AB (rats or rat or animal or animals or mouse or mice or "in vitro")

S37	S35 NOT S36
S38	Narrow by Language: - English

Recurrence and progression of periodontitis in long term care.

Appendix S6. Search strategy on CINAHL Plus EBSCOHost

CINAHL Plus EBSCOHost from 1937 to 02 May 2020

S1	(MH "Periodontitis+")
S2	(MM "Alveolar Bone Loss") OR (MM "Periodontal Attachment Loss")
S3	TI periodontit* OR AB periodontit*
S4	TI "periodont* attachment loss" OR AB "periodont* attachment loss"
S5	TI periodontal N1 pocket* OR AB periodontal N1 pocket*
S6	TI ((bleed*) N3 (probe* OR probing)) OR AB ((bleed*) N3 (probe* OR probing))
S7	TI (alveolar N2 (loss* or atroph*)) OR AB (alveolar N2 (loss* or atroph*))
S8	TI ((periodont* or alveolar) N1 resorption*) OR AB ((periodont* or alveolar) N1 resorption*)
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10	TI "supportive periodontal therap*" OR AB "supportive periodontal therap*"
S11	TI "supportive periodontal care" OR AB "supportive periodontal care"
S12	TI SPT OR AB SPT
S13	TI (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*) OR AB (periodont* or

Recurrence and progression of periodontitis in long term care.

	dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)
S14	TI "recall maintenance*" OR AB "recall maintenance*"
S15	TI "preventive maintenance" OR AB "preventive maintenance"
S16	TI ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall) OR AB ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall)
S17	(MH "Preventive Dentistry+")
S18	TI "dental prophylaxis" OR AB "dental prophylaxis"
S19	TI "oral prophylaxis" OR AB "oral prophylaxis"
S20	TI (root W0 (plane* or planing)) OR AB (root W0 (plane* or planing))
S21	TI ((dental or oral or teeth or tooth or supragingival or supra-gingival or sub-gingival or subgingival) N7 (scaling or scaler* or curettage or curette*)) OR AB ((dental or oral or teeth or tooth or supragingival or supra-gingival or sub-gingival or subgingival) N7 (scaling or scaler* or curettage or curette*))
S22	TI ((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) N1 debridement*) OR AB ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*)
S23	(MM "Diagnosis, Oral") OR (MM "Radiography, Dental") OR (MM "Radiography, Dental, Digital") OR (MM "Radiography, Panoramic")

Recurrence and progression of periodontitis in long term care.

S24	TI ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s)) OR AB ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s))
S25	TI ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or "x ray" or "ex rays")) OR AB ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or " ex ray" or exrays or x-rays or "x ray" or "ex rays"))
S26	MH ("Oral Hygiene+")
S27	TI "oral hygiene" OR AB "oral hygiene"
S28	TI mouth N2 hygiene OR AB mouth N2 hygiene
S29	TI mouth N3 care OR AB mouth N3 care
S30	TI dental N3 care OR AB dental N3 care
S31	TI care N3 teeth OR AB care N3 teeth
S32	TI oral N3 care AND AB oral N3 care
S33	TI "plaque control*" OR AB "plaque control*"
S34	TI professional N2 "plaque* removal" OR AB professional N2 "plaque* removal"
S35	TI PMPR OR AB PMPR

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S36	TI (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S37	TI ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S38	TI ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*)) OR AB ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*))
S39	(MM "Dental Care")
S40	(MM "Dental Health Education") OR (MM "Periodontal Examination")
S41	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
S42	S9 AND S41
S43	MH animals+
S44	MH (animal studies)
S45	TI (animal model*)

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S46	S43 OR S44 OR S45
S47	MH (human)
S48	S46 NOT S47
S49	S42 NOT S48
S50	Narrow S49 by Language: - English

Appendix S7. Excluded Studies

Reason for Exclusion	Publication
Insufficient follow up in supportive periodontal care	(Aeschlimann et al., 1979; Anyanechi et al., 2015; Axelsson & Lindhe, 1981; Badersten et al., 1984, 1990; Bogren et al., 2008; Bostrom et al., 1998; Brauchle et al., 2013; Chen, T.-L. et al., 2012; Cortellini, P. et al., 1996; Cortellini, P. et al., 2011; Costa et al., 2011; Dahlen et al., 1996; De Bruyckere et al., 2018; Delatola et al., 2014; Dori et al., 2013; Eickholz & Hausmann, 2002; Eickholz et al., 2019; Escribano et al., 2010; Gaspirc & Skaleric, 2007; Goel & Baral, 2017; Guarnelli et al., 2004; Hagi et al., 2015; Hakkarainen & Ainamo, 1982; Hoffmann et al., 2006; Isidor & Karring, 1986{Brauchle, 2013 #370; Iwasaki et al., 2016; Joss et al., 1994; Khoo & Newman, 1983; Lindhe & Liljenberg, 1984; Lindhe et al., 1984; Lindhe et al., 1982; Lu et al., 2018; Meinberg et al., 2001; Mengel et al., 2006; Nakao et al., 2020; Needleman & Watts, 1989; Nibali et al., 2018; Ozcelik et al., 2007; Paquette, 2005; Paul et al., 2010; Preshaw et al., 2005; Preus et al., 2017a, 2017b; Ramfjord et al., 1987b; Ramfjord et al., 1975; Ramfjord et al., 1973; Ramfjord et al., 1968; Ramich et al., 2018; Ratka-Kruger et al., 2012; Renvert et al., 1996; Renvert et al., 1990; Saito et al., 2010; Sculean et al., 2004; Shah & Kumar, 2011; Tonetti, Maurizio S. et al., 2012; Wennstrom et al., 1986; Wong et al., 2012; Yukna & Shaklee, 1993; Zuza et al., 2020)
Active periodontal therapy not presented as part of study	("American Academy of Periodontology Task Force Report on the Update to the 1999 Classification of Periodontal Diseases and Conditions," 2015; Costa et al., 2018; Franke et al., 2015; Graetz et al., 2017; Guarnelli et al., 2010; Hirschfeld & Wasserman, 1978; Jenkins et al., 2000; Jin et al., 1995; Kamma & Baehni, 2003; Martin et al., 2011; Martin et al., 2010; Mohd-Dom et al., 2014; Nyman & Lindhe, 1979; Papantonopoulos, 2004; Rudiger et al., 2019; Soder et al., 1999; Sonnenschein et al., 2018; Sugi et al., 2011; Wilson et al., 1997)
No intervention	(Aass et al., 1994; Albandar, 1990; Appukuttan et al., 2016; Beck et al., 1997; Bergstrom et al., 2000; Brignardello-Petersen, 2018a; Gatke et al., 2012; Llanos et al., 2018; Schatzle et al., 2004)

Not periodontitis cases/ Mix of cases/ specific excluded population	(Axelsson et al., 1991; Axelsson et al., 2004; Budtz-Jorgensen, 1995; Chen, X. et al., 2001; Christan et al., 2007; Gomes et al., 2019; Kim et al., 2013; Persson et al., 2007; Petersson et al., 2006; Valderhaug, 1980; Valderhaug & Birkeland, 1976; Valderhaug et al., 1993; Westfelt et al., 1996; Yu et al., 2016; Zhang et al., 2020)
Not clinical study (systematic review, review, commentary, erratum)	(Albuquerque et al., 2018; Anonymous, 1998, 2003; Anupama et al., 2019; Bonito et al., 2004; Brignardello-Petersen, 2017a, 2018b, 2019; Gaunt et al., 2008; Hodges, 2019; Ito et al., 2014a; Lang & Tonetti, 2003; Nevins, 1996; Pich, 2019; Ramfjord, 1981, 1990, 1993; Ramfjord et al., 1987a; Saxer, 2011; Schwendicke et al., 2016; Shick, 1981; Williams, 2008; Zymperdikas et al., 2020)
Unable to obtain full text	(Abu el Fadl & el Refai, 1987; Chaves et al., 1990; Günay, 1988; Ho et al., 1998; Hou et al., 1987; Itic & Serfaty, 1988; P, 2013; Pepelassi et al., 2005; Pollack, 1986; Sternig, 1985; Wilson, 1991)
Retrospective	(Bader & Boyd, 1999; Bragger et al., 1992; Brignardello-Petersen, 2017b; Carnevale et al., 2007a, 2007b; Chambrone & Chambrone, 2006; Cortellini, P. et al., 2020; Cortellini, Pierpaolo & Tonetti, 2004; Dannewitz et al., 2016; Efeoglu & Sandalli, 1996; Eickholz et al., 2007; Faggion et al., 2007; Farina et al., 2007; Goh et al., 2018; Graetz et al., 2011; Jansson & Norderyd, 2008; Matuliene et al., 2008; McGuire, 1991; McGuire & Nunn, 1996a, 1996b, 1999; Meinberg et al., 2001; Meyer-Baumer et al., 2013; Moser et al., 2002; Nibali et al., 2019; Pretzl et al., 2009; Rams et al., 1985; Ramseier et al., 2015; Saho et al., 2019; Salvi et al., 2014; Tonetti, M. S. et al., 2000; Wilson et al., 1987; Wojcik et al., 1992; Yukna & Yukna, 1997)
Case report/ series	(Bhat et al., 2018; Carnio et al., 2015; Clementini et al., 2018; Guarnieri, 2019; Heden & Wennstrom, 2006; Hu et al., 2015; Iorio-Siciliano et al., 2019; Komiya-Ito et al., 2013; Miao et al., 2016; Mros & Berglundh, 2010; Okuda et al., 2013; Silvestri et al., 2011; Siqueira et al., 2015; Tobiska & Krastl, 2018; Yanagishita et al., 2012)
Cross-sectional	(Ito et al., 2014b; Jansson et al., 2014; Lawal et al., 2015; Vaziri et al., 2016; Zhang et al., 2020)
Outcomes not relevant/ part of another study with longer follow-up	("American Academy of Periodontology Task Force Report on the Update to the 1999 Classification of Periodontal Diseases and Conditions," 2015; Fleszar et al., 1980; Nickles et al., 2009; Novaes et al., 1996)

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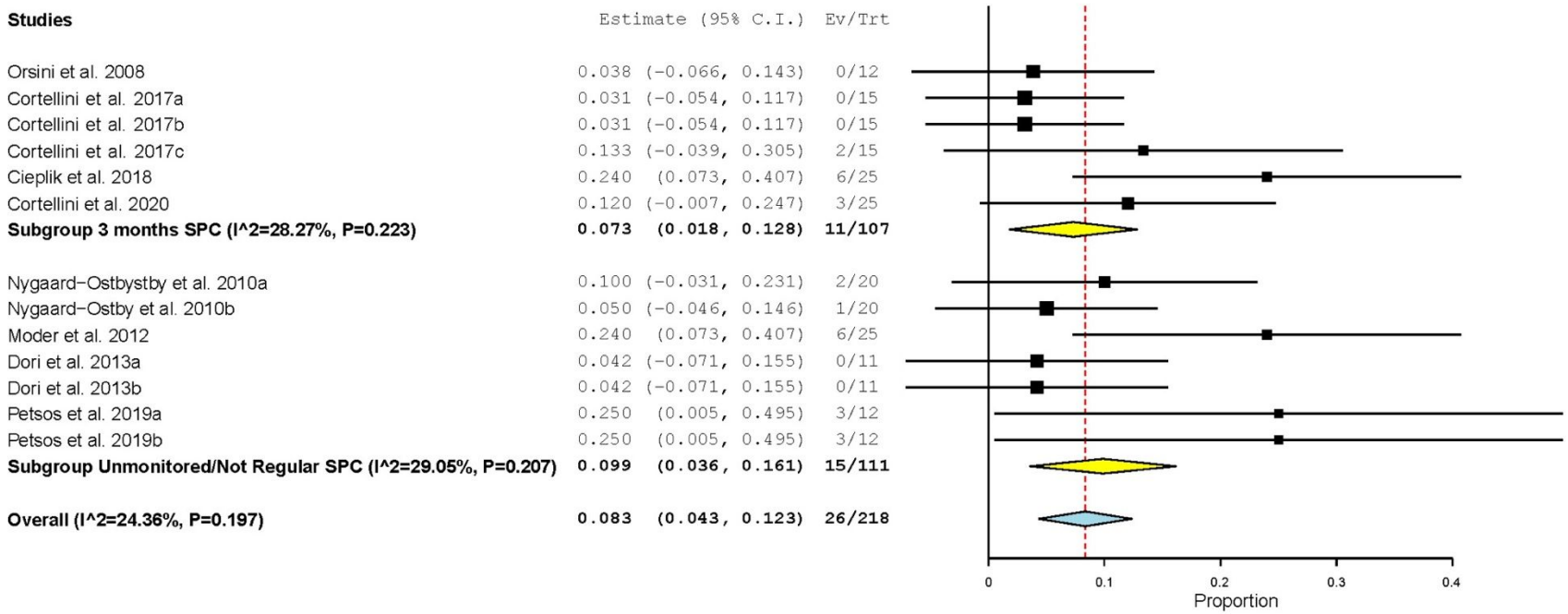
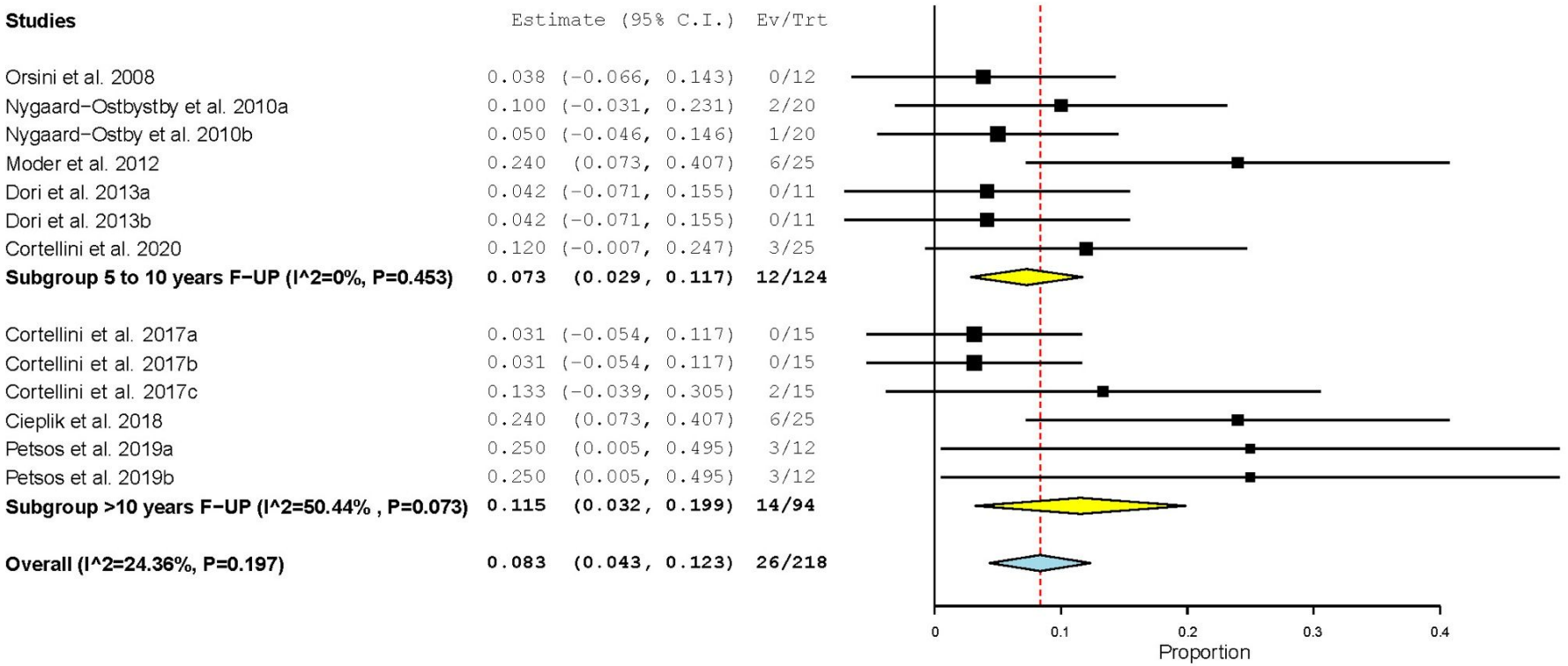
Appendix S8. Forest plot of the proportion of patients whom experienced tooth loss according to frequency of supportive periodontal care (SPC) - intention to treat.



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Appendix S9. Forest plot of the proportion of patients who experienced tooth loss according to length of follow up (intention to treat).



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e. total number of patients in the group)

Appendix S10. Focussed Question -1: Outcomes in included studies

Publication	Time-point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Axelsson & Lindhe 1981	60	1.6† (Recall) 2.6† (Non-Recall)	NR	**Non-Recall**: SPC with general dentist (1/3). **Recall**: SPC 3monthly, Univ. program (2/3). **Reason(s) for extraction:** NR **Among sites with CAL loss:** Non-Recall: 44%= ≤1 mm, 55%=2-5 mm, 1%= 6 mm Recall: 99%= ≤1 mm, 1%= 2-5 mm **FMBS†:** BL: 7%(±4.8)(Recall); 4%(±2.7)(Non-Recall) Final: 2%(±4.0)(Recall); 55%(±23.0)(Non-Recall)
Becker et al. 2001	60	0	NR	**Teeth lost:** n=6 (5-12 years) **CAL change**: not reported from after APT **GI†:** BL: 0.28(±0.63)(SRP); 0.11±0.55(Oss); 0.20±0.47(MWF) Final: 0.56±0.91(SRP); 0.43±0.55(Oss); 0.54±0.67(MWF)

Buchmann et al. 2002			**Total: 64**	
	6		8 (10.6)	
	12	NR	11 (11.2)	
	24		7 (9.7)	
	36		12 (16.3)	
	48		9 (11.7)	
	60		17 (18.3)	
Cieplik et al. 2018	156	7 (15.9%)		**Tooth loss:** Controls (n=3), Test (n=4) **Reason for extraction:** non periodontal
Cortellini et al. 2017	240	**Total: 2 (4.9%)** MPPT = 0 (0%) GTR = 0 (0%) MWF = 2 (14%)	**Total: 26** MPPT = 5 (4 pts) GTR = 6 (5 pts) MWF = 15 (8pts)	**Reasons for extraction:** Periodontitis (non-responding) **Number smokers:** n=6 (2 each treatment group) **FMBS†:** BL: 7.1%± 2(MPPT); 6% ±2.71(GTR); 7.3%±2.8 (MWF) Final: 7.1%± 22(MPPT); 7.2 %±3(GTR); 7.2%±3 (MWF)

Cortellini et al. 2020		**Total: 5 (10.4%)**	NR	**Reasons for extraction**: Unsuccessful regeneration (n=2), trauma (n=1)
	60	2 (8%)		
	120	3 (13%)		
Crespi et al. 2011		NR	NR	CAL† by initial PPD at 6 months after APT (BL) and 180-month follow-up (final): **Initial PPD** **PPD 1-4 mm** BL: 3.49±0.91(MWF); 2.40±0.76(Laser) Final: 3.88±0.23 MWF); 2.78±0.65(Laser) **PPD 5-6mm** BL: 5.50±0.53(MWF); 2.86±2.43(Laser) Final: 5.74±0.21(MWF); 2.55±1.55(Laser) **PPD >6mm** BL: 7.29±0.93(MWF); 3.98±1.12(Laser) Final: 8.23±0.63(MWF); 3.61±1.11(Laser) **GI†:** BL: 0.47±0.59(MWF); 0.52±0.54(Laser) Final: 1.07±0.62(MWF); 1.10±0.54(Laser)
Dori et al. 2013	120	0	**Total: 5 (23%)** Xeno = 2 (18%) ß-TCP = 3 (27%)	**FMBS†:** BL: 11%(Xeno); 12%(ß-TCP) Final: 17%(Xeno); 19%(ß-TCP)
Hou et al. 1997		NR	NR	Change in CAL† reported between 3 months after APT (BL) and 72 months (Final) according to tooth surface: **PPD 1-3 mm** -0.02(B); -0.19(L); -0.15(M); -0.25(D)

				PPD 4-6 mm 0.16(B); 0.07(L); 0.14(M); 0.09(D) **PPD ≥7mm** -0.07(B); 0.07(L); 0.15(M); 0.08(D)
Kaldahl et al. 1996a	84	46 (+2 roots)	See Kaldahl et al. 1996b	**Reasons for extractions/amputation:** Periodontitis. Non periodontal extractions: 27 teeth (+5 root amputations)
Kaldahl et al. 1996b	84	See Kaldahl et al. 1996a	1.24%† incidence/year	**Breakdown site** = CAL loss ≥3 mm 75% = <1.99%† incidence/year 10% = >3.0%† incidence/year (all smokers)
Knowles et al. 1979		NR	NR	**CAL† change:**. Unable to extract exact values – readers are referred to Figure 12 of the original paper.
Loesche et al. 2002		**Total: 82**		**Reasons for extraction: periodontitis**
	13.2	26	NR	13.2 months = 26 teeth extracted (17pts lost 1 tooth each, 3pts lost 2 teeth each, and 1pt lost 3 teeth)
	43.2	24		43.2 months = 24 teeth extracted (4pts lost 6 teeth each)
	61.2	32		61.2 months = 32 teeth extracted (4 pts lost 8 teeth each) **No. teeth† requiring surgery OR extraction/ pt**: 13.2 months = 1.1 43.2 months = 1.8 61.2 months = 2.36

Loesche et al. 2005	76.8	NR	NR	**No. teeth† requiring surgery OR extraction/ pt:** 76.8 months = 1.5
Moder et al. 2012	84	**Total: 8 (17%)** GTR = 4 GTR+APC = 4	**Total: 14** GTR = 5 GTR+APC = 9	Teeth lost: n=8 in 6 pts CAL defined as ≤2 mm
Nygaard-Ostby et al. 2010	120	**Total: 2** GTR = 1 Control = 1	NR	**Reasons for extraction:** periodontal (control), unknown (GTR) **BOP† (site only):** BL: 84.6%±6.5(GTR); 42.3%±12.2(Control) Final: 42.3%±12.2(GTR); 34.6%±12.9(Control)
Orsini et al. 2008	120	0	NR	**CAL†:** reported from 6 months following APT (BL) and 120 months (final): BL: 5.0±0.8mm (control); 5.2±0.7mm (test) Final: 6.0±1.1mm (control); 6.4±1.4mm (test) **FMBS†:** BL: 35%(control); 36%(test) Final:39%(control); 38%(test)
Petsos et al. 2019	240	**Total: 7** OFD = 3	**Total: 5** OFD = 2	**Reasons for extraction**: mainly non-periodontal 7 teeth lost (1pt lost 3 teeth and was a smoker, 1 pt lost 2 teeth and was a smoker, and 2 pts lost 1 tooth each)

		GTR = 4	GTR = 3	
Pihlstrom et al. 1983		NR	NR	**CAL**† reported in relation to BL and at timepoints of 6months, 1yr, 2yrs, 3yrs, 4yrs, 5.5yrs and 6.5yrs
Pihlstrom et al. 1984		**Total: 11** SRP = 5 MWF = 6		8 teeth extracted before APT finished
	27	2 (0.4%)		
	2-60	6 (1.3%)		
	61-77	3 (0.9%)		
Ramberg et al. 2001	144	1.72† (±1.0) (Test) 2.7†[a] (±3.7) (Control)	NR	**Annual CAL loss:** in both groups after the first year was small (between 0.07-0.11 mm) and similar between the two groups. **FMBS†:** BL: 24%±18(Test); 30%±19(Control) Final: 37%±12(Test); 32%±4(Control)
Rosling et al. 2001	144	1.9† (±2.2) (HSG) 0.3†[a] (±1.0) (NG)	NR	**HSG:** -**Reasons for extraction: Periodontitis**

				- 70% had >8 teeth with CAL loss ≥2mm - 34 (20%) exited study due to disease recurrence/progression **NG:** **-Reasons for extraction: non periodontal** - <10% had 8 teeth with CAL loss ≥2 mm - 7 (3%) exited study due to disease recurrence/ progression
Serino et al. 2001a	60	1.0†	NR	**Reasons for extraction: NR** **CAL loss†:** ≥0.2mm in 11 patients Cohort classed as 'downhill' patients due to recurrent disease following APT + 3yrs of APT. 12 out of 15 participants remaining were smokers. **FMBS†:** BL: 16%±18 Final: 15%±18
Serino et al. 2001b	156	1.6† (±1.7) (SRP) 0.6† (±1.1) (MWF)		**Reasons for extraction: NR** 4(14%) MWF & 8 (29%) SRP were exited from study due to disease progression **FMBS†:** BL: 18%±18(SRP); 16%%±19(MWF) Final: 30%±13(SRP); 31%±24(MWF)
	12-36		**PPD 0-3 mm:** SRP/ MWF 3.9% (±5.1)/ 2.1% (±3.5)	

	PPD≥6 mm: SRP/ MWF 7.5% (±6.4)/ 5.3% (±6.1)
36-60	**PPD 0-3 mm:** SRP/ MWF 2.8% (±4.6)/ 0.4% (±1.2) **PPD≥6 mm:** SRP/ MWF 7.8% (±8.7)/ 4.0% (±5.6)
60-156	**PPD 0-3 mm:** SRP/ MWF 2.0% (±2.5)/ 2.1% (±4.3) **PPD≥6 mm:** SRP/ MWF 2.9% (±8.2)/ 2.3% (±3.3)

† = mean values per participant

[a] = statistically significant between groups

NR: not reported, SPC: supportive periodontal care, Univ.: university, FMBS: full mouth bleeding score, BL: baseline, CAL: clinical attachment level, APT: active phase of periodontal therapy, GI: gingival index, SRP: scaling and root planing, Oss: Osseous recontouring, MWF: modified Widman flap, MPPT: modified papilla preservation technique, GTR: guided tissue regeneration, FMBS: full mouth bleeding score, Xeno: xenograft, ß-TCP: beta tri-calcium phosphate, APC: autologous platelet concentrate, PPD: periodontal probing pocket depth, B: buccal, L: lingual, M: mesial, D: distal, n: number, pt: patient, BOP: bleeding on probing, pt: patient, OFD: open flap debridement, yr: year, HSG: highly susceptible group, NG: normal group

Appendix S11. Focussed Question -2: Outcomes of Included Studies

Publication	Time-point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
Bogren et al. 2008	36	0.4† sites (Test) 0.7† sites (Control)	**CAL† gain:** 0.9 (95% CI 0.63-1.20) **PPD† reduction:** 1.2	0.7 (95% CI 0.46-0.98) 1.1	Test: 63 subjects; Control: 65 subjects Reasons for extraction: NR 70 sites lost due to extraction (25 test, 45 control) BOP: **BL** – 51% (95% CI 43.9-57.5) Test; 56% (95% CI 50.1-63.0) Control **36 months** – 32% (95% CI 25.9-38.8) Test; 38% (95% CI 328.-44.2) Control No benefit observed for test over control at 12 months.

Costa et al. 2015	60	0.6† (RC) 1.8†[a] (IC) 0.3† (RC-NST) 0.8†[a] (RC-ST) 2.2† (IC-NST) 2.8†[a] (IC-ST)	**CAL† loss % of affected sites:** Initial PPD≥4-5 mm: 13.7±1.0 (RC-ST) | 12.9±1.7 (RC-NST) Initial PPD≥6 mm: 14.7±1.2 (IC-ST) | 13.9±2.2 (IC-NST) **PPD†% of affected sites:** Initial PPD≥4-5mm: 2.9±2.9 (RC-ST) 3.2±3.1 (RC-NST) 4.2±3.5 (IC-ST) 4.4±3.8 (IC-NST) Initial PPD≥6 mm: 0.9±1.4 (RC-ST) 1.1±1.4 (RC-NST) 1.4±0.3 (IC-ST) 1.6±0.4 (IC-NST)	RC: 96 subjects; IC: 116 subjects Reasons for extraction: NR In both RC and IC groups, ST influenced greater tooth loss after 5 years. Disease recurrence – RC: 25 subjects (26.0%); IC: 42 (36.2%)[a] RC-NST: 13, RC-ST: 12, IC-NST: 17, IC-ST: 25 BOP: **BL** – 24.6±4.2% (RC); 27.8±6.1% (IC) **60 months** – 24.9±5.1% (RC); 32.8±6.9% (IC)
Jenkins et al. 2000	12	NR	**CAL† change (incl. 'loser' sites):** -0.04±0.18 (SS) -0.13±0.19 (CS) **CAL† change (excl. 'loser' sites):** 0.11±0.20 (SS) 0.20±0.18 (CS)	CS: 17 subjects; SS: 14 subjects 'Loser' sites (CAL loss ≥2mm): n=21(SS); n=21(CS) BOP (all sites):

			PPD† change (incl. 'loser' sites): 0.37±0.15 (SS) 0.59±0.13(CS) **PPD† change (excl. 'loser' sites):** 0.45±0.18 (SS) 0.65±0.14 (CS)	**BL** - 47±7% (CS); 48±0.06%(SS) **12 months** - 58±6% (CS); 56±6%(SS) No benefit observed for test over control at 12 months.
Killeen et al. 2018	24	3 (Test=1 Control=2)	**CAL† gain:** 0.8±0.9 1.0±0.7 **PPD† reduction:** 0.8±0.9 1.0±0.6	Test: 27 subjects; Control: 28 subjects No benefit observed for test over control at 24 months.
Lulic et al. 2008	12	0	**CAL† change:** -0.09±0.41 -0.20±0.61 **PPD† reduction:** -0.27±0.43 -0.07±0.61	Test: 5 subjects (39 sites); Control: 5 subjects (31 sites) BOP (test sites only): **BL** - 97% (test); 84%(control) **12 months** - 77% (test); 87%(control) No benefit observed for test over control at 12 months.

Tonetti et al. 2012	12	NR	**PPD† change (relative to BL PPD):** Initial PPD 4 mm: 0.58 0.57 Initial PPD 5 mm: 1.09 0.98 Initial PPD 6 mm: 1.34 1.26 Initial PPD 7 mm: 1.63 1.70 Initial PPD >8 mm: 2.09 2.23	Test: 100 subjects; Control: 102 subjects 'Loser' sites (CAL loss ≥2 mm): 15 subjects (7.5%) (excluded) – 8 (Test); 7(Control) Adverse events: 34 subjects with 56 events (Test) 49 subjects with 75 events (Control) No benefit observed for test over control at 12 months.

† = mean values per participant

[a] = statistically significant between groups

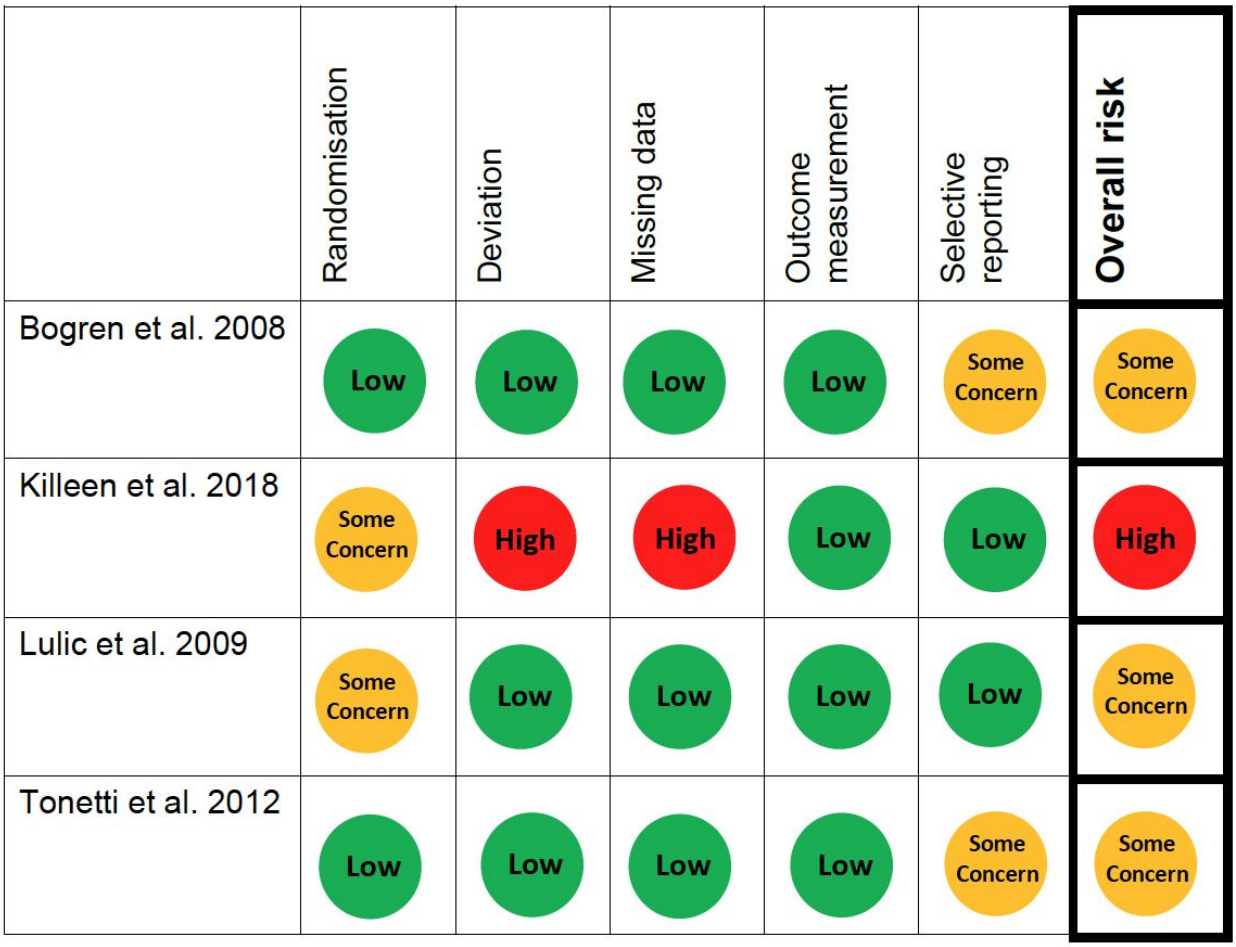
CAL: clinical attachment level, PPD: periodontal probing pocket depth, NR: not reported, 95% CI: 95% confidence interval, NST: non-surgical therapy, ST: surgical therapy, BOP: bleeding on probing, BL: baseline, RC: regular compliers, IC: irregular compliers, gp: group, SS: subgingival scaling group, CS: coronal scaling group

Appendix S12. Newcastle-Ottawa Scale for assessing the quality of non-randomised, non-interventional studies.

Publication	Selection (maximum = 3★)	Exposure/ Outcome (maximum = 3★)
Axelsson & Lindhe 1981	★★★	★★
Becker et al. 2001	★★★	★★
Buchmann et al. 2002	★★★	★★
Cieplik et al. 2018	★★★	★★★
Cortellini et al. 2017	★★★	★★★
Cortellini et al. 2020	★★★	★★★
Crespi et al. 2011	★★★	★★
Dori et al. 2013	★★★	★★
Hou et al. 1997	★★★	★
Kaldahl et al. 1996a	★★★	★★★
Kaldahl et al. 1996b	★★★	★★★
Knowles et al. 1979	★★★	★★
Loesche et al. 2002	★★	★★
Loesche et al. 2005	★★	★★★
Moder et al. 2012	★★★	★★
Nygaard-Ostby et al. 2010	★★★	★★

Orsini et al. 2008	★★★	★★
Petsos et al. 2019	★★★	★★
Pihlstrom et al. 1983	★★★	★★★
Pihlstrom et al. 1984	★★★	★★★
Ramberg et al. 2001	★★★	★★★
Rosling et al. 2001	★★★	★★★
Serino et al. 2001a	★★	★★★
Serino et al. 2001b	★★★	★★★

Appendix S13. Cochrane Risk of Bias Tool 2.0 for assessing the quality of randomised controlled trials.



Appendix S14. Robins-I tool for assessing the quality of interventional non-randomised controlled trials/ prospective cohorts.

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	**Overall risk**
Costa et al. 2015	Serious	Low	Serious	Low	Low	Serious	NI	Serious
Jenkins et al. 2000	Moderate	Low	Serious	Low	NI	Serious	NI	Serious

NI = No Information

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	88-103
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	47-83
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	28
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12, 40
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1-4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 7-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 5-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-17
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	15-17
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

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RECURRENCE AND PROGRESSION OF PERIODONTITIS AND METHODS OF MANAGEMENT IN LONG TERM CARE. A SYSTEMATIC REVIEW AND META-ANALYSIS.

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RUNNING TITLE

Recurrence and progression of periodontitis in long term care.

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ABSTRACT

Aims: To systematically review the literature to evaluate the recurrence of disease of people in long-term supportive periodontal care (SPC), previously treated for periodontitis, and determine the effect of different methods of managing recurrence. The review focussed on stage IV periodontitis.

Methods: An electronic search was conducted (until May 2020) for prospective clinical trials. Tooth loss was the primary outcome.

Results: Twenty-four publications were retrieved to address recurrence of disease in long-term SPC. Eight studies were included in the meta-analyses for tooth loss, and three studies for disease progression/recurrence (clinical attachment level [CAL] loss≥2 mm). For patients in SPC 5-20 years, prevalence of losing ≥ one tooth was 9.6% (95% confidence interval [CI] 5-14%), whilst experiencing ≥ one site of CAL loss≥2 mm was 24.8% (95% CI 11-38%). Six studies informed on the effect of different methods of managing recurrence, with no clear evidence of superiority between methods. No data was found specifically for stage IV periodontitis.

Conclusions: A small proportion of patients with stage III/IV periodontitis will experience tooth loss in long-term SPC (tendency for greater prevalence with time). Regular SPC appears to be important for reduction of tooth loss. No superior method to manage disease recurrence was found.

CLINICAL RELEVANCE

Scientific rationale for the study: Supportive periodontal care (SPC) is a life-long commitment for the periodontitis patient and for dental professionals taking care of them. Prior to embarking on treatment of periodontitis, patients and dental professionals should understand the likelihood of disease recurrence/progression during SPC and the costs and harms of retreatments during SPC.

Principal findings: Patients in long term routine SPC programmes should expect a low mean prevalence of tooth loss, however disease recurrence/ progression may occur.

Practical implications: The importance of regular SPC recall visits should be emphasised to patients originally treated for stage III/IV periodontitis in order to reduce the risk of tooth loss.

1. INTRODUCTION

Periodontitis is defined as a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and progressive destruction of the tooth-supporting apparatus (Papapanou et al. 2018). It is thought to be the sixth most prevalent condition in the world with severe forms of the disease affecting 7-11% of adults world-wide (Kassebaum et al. 2014, Kassebaum et al. 2017).

Treatment of periodontitis consists of an active periodontal therapy (APT), which often begins with the first step of therapy (Sanz et al. 2020) which includes addressing modifiable risk factors such as tobacco use and glycaemic control in people with diabetes, along with building the skills and behaviours related to effective daily plaque removal (Newton and Asimakopoulou 2018, Carra et al. 2020, Ramseier et al. 2020). Furthermore, when periodontal pockets are established, operative treatments such as non-surgical therapy (subgingival instrumentation - part of the second step of therapy) and surgical options (open flap debridement, resective and regenerative surgery – part of the third step of treatment) are required (Sanz-Sanchez et al. 2020). On completion of APT, ongoing maintenance care, known as supportive periodontal care (SPC) is thought to be essential in minimising disease progression or recurrence (Rosling et al. 2001, Matuliene et al. 2008, Trombelli et al. 2015).

SPC is a complex intervention and may be seen as the fourth step of therapy (Sanz et al. 2020). It is a life-long phase of care, and requires on-going commitment from the patient in order to reduce risk of disease progression and subsequently prevent tooth loss (Lee et al. 2015) and maintain oral health and related quality of life (Armitage and Xenoudi 2016).

Recent systematic reviews have shown that there is limited evidence to advocate the superiority of any one approach to improve tooth maintenance during SPC (Manresa et al. 2018), and that clinical attachment levels (CAL) appear to remain stable over the long term for patients in SPC (Sanz-Martin et al. 2019). Encouragingly, the evidence also suggests that mean annual tooth loss due to periodontitis during SPC of up to 14 years is low (Rosling et al. 2001, Trombelli et al. 2015), however following the 11th European Workshop in Periodontology, it was identified that more research was required to plug

gaps in the evidence, particularly regarding treatments which work best in the phase of SPC (Sanz et al. 2015). A conclusion strengthened by a recent Cochrane review (Manresa et al. 2018).

What is less clear from previous reviews is what patients might expect in terms of recurrence of the condition and the effect of different treatment methods of managing recurrence, which may be considered in terms of stabilising recurrence and preventing tooth loss, associated costs and effect on quality of life.

Thus, in view of the gaps in the evidence and its importance both from a public health consideration as well as the perspective of the individual patient, the purpose of this systematic review was to 1) systematically review the evidence for the recurrence of periodontitis during long term supportive periodontal care; and 2) to identify the effect of different methods of managing recurrence.

1.1 Objectives

1.1.1 Focussed Questions (FQ)

The two questions which we sought to answer were focussed question 1 (FQ-1): 'In people treated for periodontitis and in SPC for five years or more, compared with no or irregular SPC, how common is recurrence of the condition?' and, focussed question 2 (FQ-2): 'In people experiencing recurrence of periodontitis, what is the effect of different methods of treatment of the recurrence as assessed by measures of health, quality of life, cost and accessibility of care and harms?'.

1.1.2 PICOS Components

Population

Participants treated for periodontitis with no age restriction. Any definition of periodontitis was included considering there have been a number of changes in the classification of periodontal diseases over recent decades. No restriction was applied for the type of treatments carried out both in the APT or supportive periodontal care phases. The end of active treatments was clearly defined in terms of periodontal health status. The focus of the workshop for which this review was commissioned was stage IV periodontitis (advanced disease with extensive tooth loss) (Tonetti et al. 2018). However, in view of

both the recent adoption of this classification and our expectation that severity of periodontitis would be incompletely described, we included all severities of periodontitis with a plan to analyse stage IV periodontitis separately if possible.

Intervention

Any kind of intervention that might be considered part of SPC. As SPC is a complex intervention, for the purposes of this review this may have included;

- Interview: periodontal health symptoms, medical and social history, risk factors including tobacco use, stress and diabetes and reported plaque control regime
- Assessment: plaque and calculus deposits, periodontal health including inflammation, probing pocket depths and bleeding pockets
- Formulating: intervention needs including risk factor management, oral hygiene and retreatment
- Practical Intervention: oral hygiene coaching, instrumentation of supra- and subgingival plaque and calculus, treatment of sites with recurrence (finding of periodontitis at a previously healthy/stable site) or residual periodontitis (a deep periodontal pocket remains despite active therapy) (Graziani et al. 2018).
- Planning: interval before next SPC visit

Comparison

Studies comparing SPC with no/irregular SPC, different frequencies of SPC recall visits, different settings for SPC (specialist versus non-specialist) and SPC using adjuncts (e.g. chemical agents, locally administered antiseptics/ antibiotics and systemically administered antibiotics).

Outcome Measures

It would be impossible to distinguish the published literature between recurrence, occurrence of disease at previously healthy (non-diseased) sites and progression of residual disease at unstable sites. Recurrence means a finding of periodontitis at a site that was rendered periodontally healthy/ stable through treatment. Occurrence refers to a site within a patient diagnosed and treated for periodontitis (periodontitis case) but which did not previously show signs of disease, and progression would be characterised by deterioration (e.g. CAL loss) at a site that had residual disease despite active treatment.

Since we could not make the distinction from the existing literature, the primary outcome measure for this systematic review was the proportion of patients who experienced tooth loss. Secondary outcomes were 1) proportion of patients whom experienced at least one site of CAL loss of 2 mm or greater; 2) number of periodontal probing pocket depths (PPD) of at least 5 mm or more with bleeding on probing; 3) number of sites that need/ experienced retreatment; 4) change in oral health related quality of life (OHQOL) with a validated OHQOL tool; 5) health economic outcomes; 6) any other patient reported outcomes (PRO).

Study Design

The search strategy included clinical studies with a prospective design (for both FQ-1 and FQ-2) in order to minimise selection bias. As FQ-2 was an intervention research question, studies were limited to randomised controlled trials, controlled trials and prospective cohorts.

2. METHODS

2.1 Protocol Development and Registration

This protocol was evaluated and approved by the Scientific Committee of the XVII European Workshop on Periodontology and was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al. 2009). Details of the protocol for this systematic review were registered on PROSPERO (Unique ID: CRD42020176451).

2.2 Patient Involvement

This review was co-produced with a member of the British Society of Periodontology Patient Forum who contributed to design, interpretation and publication.

2.3 Eligibility Criteria

To conduct this systematic review, we searched for all studies which had included treatment for periodontitis and had a minimum of 5 years following the end of the APT.

2.4 Literature Search

2.4.1 Electronic Search

A sensitive search strategy was formulated with an experienced librarian (DM) with consideration of previous systematic reviews related to this topic (Trombelli et al. 2015, Manresa et al. 2018, Sanz-Martin et al. 2019) using a string of medical subject headings and free-text terms (see Appendix S1-S6). The search strategies were modelled on that devised for the MEDLINE database and subsequently modified for other databases as was needed. The search was restricted to the English language (to harmonise methods across all reviews being conducted for the European Workshop and due to time constraints) and results were downloaded to EndNote X9 (2013).

Electronic databases searched included;

Ovid MEDLINE (1946 -1 May 2020) (Appendix S1);

Ovid EMBASE Classic and EMBASE (1947 – 1 May 2020) (Appendix S2);

LILACS VHL Regional Portal (to 2 May 2020) (Appendix S3);

Cochrane Central Register of Controlled Trials (CENTRAL) (to 2 May 2020) (Appendix S4);

Dentistry and Oral Sciences Source EBSCOHost (to 2 May 2020) (Appendix S5);

CINAHL Plus EBSCOHost (1937 – 2 May 2020) (Appendix S6)

OpenGrey was searched for grey literature and the register of clinical studies at the US National Institutes of Health (www.clinicaltrials.gov) in order to identify unpublished studies which may be relevant.

2.5 Study Selection

2.5.1 Inclusion Criteria

In regard to FQ-1, the following inclusion criteria were applied:

- prospective studies (to minimise the risk of selection bias)

- minimum follow-up of 5 years in SPC (to consider outcome of disease progression/ recurrence)
- endpoint of APT and the start of SPC clearly defined

For FQ-2, the following inclusion criteria were applied:

- prospective studies
- minimum follow-up of 12 months

2.5.2 Exclusion Criteria

The following exclusion criteria were applied:

- Cross-sectional studies
- Retrospective studies
- Case- series

  To distinguish between case-series and cohort studies (particularly with low numbers of participants), a key characteristic for exclusion was a lack of information on the method of enrolment/ participant selection (e.g. consecutive cases).
- Studies which investigated solely specific systemic disease or risk factors (e.g. smoking, diabetes) or only recruited participants for periodontitis treatment or previously treated for periodontitis

2.5.3 Screening

Titles and abstracts (if available) retrieved from the searches were screened by a combination of two review authors (NL, FM and SH), in duplicate and independently. Based on titles and abstracts, irrelevant studies were discarded. Full texts were obtained for the remaining studies and included those which had insufficient information in the title and abstract and if at least one reviewer included the study for the next phase of screening. Reference lists of all studies that were included for full text screening and previous reviews were screened for missing records.

Two reviewers (NL and FM) assessed the full text reports according to the inclusion criteria, in duplicate and independently. Disagreements were resolved by discussion and a third author was consulted (IN) when agreement could not be resolved. Where there were several publications from the same original study, we included the study with the

longest follow up period for the relevant outcome measure. Studies that did not meet the eligibility criteria were excluded and specified reasons for exclusion (Appendix S7).

2.6 Data Collection

2.6.1 Data Extraction

Data were extracted by two review authors (NL and FM), in duplicate and independently using a data extraction form on Microsoft® Excel. Disagreements were resolved by discussion and when resolution was not possible, a third reviewer was consulted (IN). In order to clarify missing or unclear data, authors were contacted (where possible).

2.6.2 Risk of Bias

Quality assessment was carried out by two review authors (NL and SH), in duplicate and independently. Regarding FQ-1, studies were assessed for risk of bias in relation to the phase of SPC. The included studies were assessed as prospective cohorts using a modified version Newcastle-Ottawa scale (NOS) (Wells et al. 2011) to account for single arm cohorts. The modified version of the NOS removed questions concerning control groups, therefore two domains, selection and outcome, were assessed with a maximum score possible of six. FQ-2 included studies were assessed for risk of bias using the Cochane RoB 2.0 tool (Sterne et al. 2019) for interventional randomised controlled trials (RCT), ROBINS-I tool (Sterne et al. 2016) for interventional non-randomised controlled trials (CCT) and cohorts.

2.7 Data Synthesis

Data were entered into tables stratified by study design, and decisions on which studies to include in a meta-analysis was made depending on the similarity of chief study characteristics related to each research question (i.e. incidence of recurrence or methods of managing recurrence).

Evaluation of the included studies displayed substantial heterogeneity between publications in regard to design and reporting of outcomes in the SPC phase and in trials addressing treatment methods for disease recurrence. A qualitative report of the data was planned for those studies that could not be included in the meta-analyses.

2.8 Data Analysis

The number of events on the total number observed at the final assessment was used for the meta-analyses. To avoid under-estimating both tooth loss and CAL loss≥2 mm, we decided to use the 'per protocol' number of participants. Numerous studies reported tooth loss per participant at the end of the study. An intention to treat approach would not be able to account for tooth loss associated with subjects during follow up, and thus risk under-estimating average tooth loss. In order to check this, an intention to treat analysis (ITT) was carried out for the primary outcome of tooth loss.

Data were grouped with respect to a) frequency of SPC, 3 monthly (3M) or unmonitored/irregular (IRREG) and; b) length of follow-up (FU), 5-10 years follow-up (5-10 FU) or greater than 10 years follow-up (>10 FU). Meta-analyses were subsequently performed to determine an overall prevalence of tooth loss (primary outcome) and CAL loss (≥2 mm) (secondary outcome) at patient level. The number of events on the total number observed (per protocol) were entered into the statistical software. In regard to tooth loss, this was the number of patients who lost at least one tooth, on the total number of patients available at follow-up. For CAL loss, this was the number of patients experiencing CAL loss≥2 mm at a minimum of one site, on the total number of patients available at follow-up. In the meta-analyses, 'clusters' were formed in each subgroup (Salvi et al. 2018). One cluster was representative of one treatment arm in APT. Therefore, studies with multiple treatment arms, contributed more than one cluster. Open source software, OpenMeta[Analyst] (Wallace et al. 2012), was used for meta-analysis, and a binary random-effects model chosen. Weighted mean values and 95% confidence intervals (CI) are presented via Forest plots. A p value of <0.05 was considered statistically significant.

The degree of statistical heterogeneity between studies was assessed using the chi-square test and quantified utilising the I^2 statistical test. Subgroup and meta-regression analyses were performed to determine the effect of: a) the type of treatment in APT either regenerative (reg) or non-regenerative (non-reg), b) frequency of SPC, 3 monthly or IRREG and; c) length of follow-up, 5-10 years or greater than 10 years on tooth loss and CAL loss ≥2 mm and expressed as coefficients (COEF) and 95% confidence intervals. Meta-analysis was stratified into subgroups of reg and non-reg surgery to allow

evaluation of potential differences in outcomes. The summary estimate includes both types of therapy combined.

Interpretation of the I^2 test was according to the guidance of the Cochrane Handbook (Deeks et al. 2019), as follows:

- 0% to 40%: might not be important
- 30% to 60%: moderate heterogeneity
- 50% to 90%: substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Studies that could not be included in the meta-analysis were described in a narrative form and an attempt to triangulate qualitative results with that of the meta-analysis was made to assess consistency of data.

Kappa statistic was used to assess the reviewer agreement based on full-text screening, and the score interpreted using values suggested by Cohen (1960). The reviewers were calibrated with the first 10 full text publications.

3. RESULTS

3.1 Study Selection

The search yielded a large number of records, confirming a high sensitivity and low specificity which reflected the search strategy. Based on the definition of stage III versus stage IV periodontitis (Tonetti et al. 2018), we were unable to restrict the studies to solely stage IV periodontitis cases. Studies screened gave no detail of reasons for previous extraction(s) and most used previous classifications for defining included cases. Additionally, there was a lack of studies which specifically addressed recurrence in SPC.

A total of 31,303 records were found through the electronic searches, and following removal of duplicates, 14,860 remained (Figure 1). Following screening of titles and abstracts, 228 titles remained for full-text evaluation. Subsequently, 204 studies were

excluded (Appendix S7) for often more than one reason, however the main reason was generally recorded.

FQ-1

24 studies (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Hou et al. 1997, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Crespi et al. 2011, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020) were included in the qualitative and quantitative analysis (Tables 1 and 2).

Studies reporting on the same population were included if each paper reported on a different but relevant outcome important for this systematic review (Pihlstrom et al. 1984, Kaldahl et al. 1996b) (Table 2). The kappa score for FQ-1 was calculated to be 0.81 for full-text screening agreement indicating almost perfect agreement (Cohen 1960).

FQ-2

Six studies were included (Jenkins et al. 2000, Bogren et al. 2008, Lulic et al. 2009, Tonetti et al. 2012, Costa et al. 2015, Killeen et al. 2018) (Tables 3 and 4). These were qualitatively analysed due to heterogeneity particularly in types of intervention. The kappa score for full-text screening for FQ-2 was calculated to be 0.62 indicating substantial agreement (Cohen 1960).

3.2 Population

We were unable to find data on stage IV periodontitis or that could be analysed as such. Studies reported an initial diagnosis of periodontitis with some further describing as moderate and severe disease. Types of diagnosis reported in the articles included, ‘advanced periodontal disease’, ‘moderate to advanced adult periodontitis’, ‘aggressive periodontitis’, ‘chronic periodontitis’, ‘advanced chronic periodontitis’, and ‘severe chronic periodontitis’. One recently published study (Cortellini et al. 2020) referred to the population as, ‘stage III or IV periodontitis’ in a retrospective manner, as recruitment was prior to the publication of the most recent classification (Table 1).

3.3 Supportive Periodontal Care

3.3.1 Description of SPC

When assessing the elements carried out in the phase of SPC, the majority of studies included brief description of oral hygiene review and re-enforcement in conjunction with focussed supra- and subgingival instrumentation (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Hou et al. 1997, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Crespi et al. 2011, Dori et al. 2013, Cortellini et al. 2017). Five publications did not describe any detail about recall visits (Knowles et al. 1979, Moder et al. 2012, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020).

Nine studies provided some description of the operator(s) who carried out the SPC visits (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1984, Rosling et al. 2001, Loesche et al. 2002, Loesche et al. 2005, Nygaard-Ostby et al. 2010, Cortellini et al. 2017, Cieplik et al. 2018) although level of experience was not advised.

No studies specifically addressed risk factor control in regard to smoking cessation or glycaemic control advice. Details of the factors which influenced recall interval length were not given in any study.

3.3.2 Recall Intervals

All studies reported on the frequency of recall intervals, with the majority of studies applying 3 monthly visits. However, there was some variability between studies, with the shortest interval being 1-3 months (Hou et al. 1997) and the longest being up to 12 months (Rosling et al. 2001), based on a perceived disease risk by the attending dentist (details not specified). Some studies reported a more frequent recall plan in the first 1-2 years after APT (Axelsson and Lindhe 1981, Buchmann et al. 2002, Moder et al. 2012, Cieplik et al. 2018), thereafter reducing the frequency with tailored SPC intervals.

3.3.3 Length of Follow-Up

The minimum follow-up period in SPC to be included in this review was 5 years. Seventeen studies had a follow-up of 5-10 years (Knowles et al. 1979, Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996a, Kaldahl et al. 1996b, Hou et al. 1997, Becker et al. 2001, Serino et al. 2001a, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005, Orsini et al. 2008, Nygaard-Ostby et al. 2010, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2020). Seven studies (Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001b, Crespi et al. 2011, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019) had SPC follow-up periods greater than 10 years. Two studies reported on 20 years of follow-up (Cortellini et al. 2017, Petsos et al. 2019).

3.4 Meta-Analyses

3.4.1 Tooth Loss

Eight studies addressing FQ-1 contributed data for estimating tooth loss at patient level (Orsini et al. 2008, Nygaard-Ostby et al. 2010, Moder et al. 2012, Dori et al. 2013, Cortellini et al. 2017, Cieplik et al. 2018, Petsos et al. 2019, Cortellini et al. 2020). Data were sub-grouped according to treatment arms in APT, culminating in a) six clusters for patients in the 3M subgroup and seven clusters in the IRREG subgroup; and b) seven clusters for patients in the 5-10 FU subgroup and six clusters in the >10 FU subgroup. The per protocol meta-analysis at patient level for tooth loss, observed 192 participants (Figure 2).

The 3M subgroup included 98 participants, whilst the IRREG subgroup observed 94. The proportion of patients experiencing tooth loss overall yielded a weighted value of 9.6% (95% CI 5-14%), with low heterogeneity I^2=28% (p=0.161). Subgroup analysis showed a weighted mean value for the 3M group as 8% (95% CI 2-14%), with low-moderate heterogeneity I^2=32% (p=0.195), whilst the IRREG group displayed a 11.9% (95% CI 5 - 19%) prevalence, low-moderate heterogeneity I^2 30.2% (p=0.198).

The ITT meta-analysis included a total of 218 participants (Appendix S8). The 3M subgroup had 107 patients, and the IRREG subgroup included 111. As anticipated, the percentages were less than the per protocol analysis. Overall, the proportion of patients

experiencing tooth loss was 8.3% (95% CI 4.3-12.3%) and low heterogeneity (I^2=24%, p=0.197). The subgroup analysis found that the 3M group displayed a prevalence of 7.3% (95% CI 1.8-12.8%) and low heterogeneity, I^2=28% (p=0.223), whilst the IRREG group was 9.9% (95% CI 3.6-15.1%) with low heterogeneity once again, I^2=29% (p=0.207).

Length of follow-up time was also considered at patient level for tooth loss (Figure 3), 106 participants were observed in the 5-10 FU subgroup and 86 in the >10 FU subgroup. The weighted value for tooth loss was 8.2% (95 CI 3%-13%) for the 5-10 FU group and 12.7% (95% CI 4-22%) for >10 FU group, with substantial heterogeneity I^2 test 70% (p=0.374) and 51% (p=0.070) respectively.

The ITT analysis according to follow-up time at patient level (Appendix S9) observed 124 participants in the 5-10 FU subgroup and 94 in the >10 FU subgroup. The proportion of patients experiencing tooth loss for the 5-10 FU group was 7.3% (95% CI 2.9-11.7%) and for the >10 FU group was 11.5% (95% CI 3.2-19.9%), with no heterogeneity detected I^2=0% (p=0.453) and substantial heterogeneity I^2 test 50% (p=0.073) respectively.

Meta-regression analyses were performed to investigate the influence of type of treatment in APT (regenerative or non-regenerative), frequency of SPC (3M or IRREG) and length of follow-up (5-10 FU or >10 FU) on tooth loss. There was no evidence of an association between type of treatment (COEF 0.1; 95% CI -0.07 – 0.3, p=0.249), frequency of SPC (COEF 0.05; 95% CI - 0.05 - 0.1, p=0.341) or length of follow-up (COEF 0.02; 95% CI -0.08 – 0.1, p=0.704) and tooth loss was found.

3.4.2 Clinical Attachment Level loss (≥2 mm)

Three studies for FQ-1 contributed data for estimating the number of patients experiencing CAL loss ≥2 mm (Dori et al. 2013, Cortellini et al. 2017, Petsos et al. 2019). Data were sub-grouped according to treatment arms in the APT, culminating in a) three clusters for patients in the 3M subgroup and four clusters in the IRREG subgroup; and b) two clusters for patients in the 5-10 FU subgroup and five clusters in the >10 FU subgroup. The meta-analysis for patients experiencing CAL loss ≥2 mm, observed 86 participants (Figure 4).

The 3M subgroup observed 41 participants, whilst the IRREG subgroup observed 45. The proportion of patients experiencing at least one site of CAL loss≥2 mm overall yielded a weighted mean value of 24.8% (95% CI 11-38%), with substantial heterogeneity I^2 =63% (p=0.013). Subgroup analysis showed a weighted mean value for the 3M group as 30.2% (95% CI -2-63%), I^2 = 87% (p<0.0001), whilst the IRREG group displayed a 21.4% (95% CI 10-33%) prevalence, I^2 0% (p=0.884). The difference between the groups was not statistically significant (p=0.332).

Length of follow-up time was assessed at a patient level for CAL loss ≥2 mm (Figure 5), with 22 participants observed in the 5-10 FU subgroup and 64 in the >10 FU subgroup. The proportion of patients experiencing at least one site of CAL loss ≥2 mm was 22.1% (95% CI 5-39%) for the 5-10 FU group and 26.3% (95% CI 8-45%) for >10 FU group I^2 = 0% (p=0.609) and 75% (p=0.003) respectively.

The random effects meta-regression analyses found no association between frequency of SPC (COEF 0.13; 95% CI -0.1 – 0.4, p=0.332) and length of follow-up (COEF -0.16; 95% CI -0.5 – 0.2, p=0311) with percentage of patients experiencing CAL loss≥2 mm, however the type of treatment carried out in APT (regenerative or non-regenerative) was significantly associated (COEF 0.26; 95% CI 0.01 – 0.5, p=0.043), whereby a non-regenerative intervention was more likely to experience greater proportion of patients with CAL loss≥2 mm. Therefore, the estimate of the prevalence of patients with CAL loss≥2 mm would be expected to increase by 0.26 when non-regenerative treatment was carried out in APT according to this random effects meta-regression model.

3.5 Qualitative Analyses

3.5.1 Tooth Loss

FQ-1

Tooth loss was reported in 17 studies, however due to substantial heterogeneity in reporting of this outcome, nine studies could not be included in the meta-analyses (Axelsson and Lindhe 1981, Pihlstrom et al. 1984, Kaldahl et al. 1996a, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Loesche et al. 2002) and are described in a narrative form (Appendix S10).

One study (Loesche et al. 2002) with regular 3 monthly SPC and a follow-up of a median of 61.2 months, reported the proportion of patients with tooth loss as being 56.8%. This is substantially higher than that estimated for the 3M subgroup analyses (8.0%, 95% CI 1.9-14.1%) and 5-10 FU subgroup (8.2%, 95% CI 3.0-13.4%). Additionally, the authors reported a substantial drop out rate of 46 participants from the original 90 subjects who entered the maintenance phase. On the other hand, one other small split-mouth study (Becker et al. 2001) reported the prevalence as 0% over the course of 5 years.

A number of studies reported mean tooth loss over the course of SPC (Axelsson and Lindhe 1981, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b). Some studies did not report the reasons for extraction and, so as to prevent under-estimation of tooth loss, were included in the summary (Appendix S10). Other studies reported absolute numbers of teeth lost (Pihlstrom et al. 1984, Kaldahl et al. 1996a).

For studies with a 5-10 FU (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Becker et al. 2001, Serino et al. 2001a, Buchmann et al. 2002, Loesche et al. 2002, Loesche et al. 2005), average tooth loss per patient ranged from 0 - 2.6 teeth, whilst for studies with >10 FU (Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001b), this ranged from 0.6 (±1.1) to 2.7 (±3.7) teeth per patient.

Studies which performed regular 3-4 monthly SPC (Axelsson and Lindhe 1981, Pihlstrom et al. 1983, Pihlstrom et al. 1984, Kaldahl et al. 1996b, Kaldahl et al. 1996a, Becker et al. 2001, Ramberg et al. 2001, Rosling et al. 2001, Serino et al. 2001a, Serino et al. 2001b, Loesche et al. 2002, Loesche et al. 2005) reported mean tooth loss ranging from 0 to 2.7 or absolute numbers of teeth lost (from the cohort) in the range of 8 - 46 (+2 roots) over the course of SPC.

FQ-2

One RCT (Bogren et al. 2008) and one prospective cohort (Costa et al. 2015) reported on tooth loss in patients previously treated for moderate to advanced periodontitis in SPC with unstable disease (Appendix S11).

Bogren et al. (2008) compared locally delivered 8.8% doxycycline gel applications (every 3 months) with scaling and root planing (SRP) in 63 participants (test) in sites of PPD≥5 mm to SRP alone (control) in 65 participants. The study reported 25 lost sites due to tooth extraction (mean of 0.4 sites/participant) in the test group compared with 45 lost sites (mean 0.7 sites/ participant) in the control group over a 3-year follow-up period with routine 6 monthly SPC. The difference was not statistically significant ($p>0.05$) between treatment groups.

A prospective cohort study (Costa et al. 2015) analysed a population of 212 individuals over a 5-year period and retrospectively divided the cohort into two groups according to SPC visit compliance. 96 regular compliers (RC) and 116 IRREG compliers (IC) were subject to non-surgical therapy (NST) and, if deemed necessary, surgical therapy (ST) (if persistent PPD≥5 mm were detected). Mean tooth loss was reported to be 0.6 and 0.8 for RC and IC respectively. The difference was found to be statistically significant ($p<0.05$). Tooth loss was also assessed according to treatment modality within each compliance group. The RC group demonstrated a mean tooth loss of 0.3 (NST) and 0.8 (ST), compared with the IC group, which was 2.2 and 2.8 for NST and ST respectively. The differences between groups for both NST and ST were statistically significant. Interestingly, in both RC and IC groups, ST influenced greater tooth loss after 5 years.

3.5.2 Sites with CAL loss≥2 mm

FQ-1

The majority of studies reported mean or median CAL over the duration of SPC. Some studies reported sites experiencing mean CAL loss≥2 mm as frequency distributions at various timepoints in SPC or in relation to initial PPD (prior to APT).

One study (Buchmann) of 13 participants reported the prevalence of disease progression over a 5 year follow-up at various timepoints. This study reported total of 64 sites which experienced disease progression and it was not clear whether these sites were recurrent or newly occurrent. The greatest number of sites experiencing disease progression occurred at 60 months, where 17 sites (18.3%) experienced CAL loss≥2 mm, followed by 12 sites (16.3%) which occurred at 36 months.

Another study (Kaldahl et al. 1996b) reported 'breakdown' sites where attachment loss was ≥3 mm. This group found a mean incidence per year of 1.24% over the course of 84 months of routine 3 monthly SPC. Of interest, a small proportion of participants (10%) accounted for a mean of more than 3.0% incidence per year, and these were all smokers.

Moder et al. (2012) conducted a split mouth study over 72 months of SPC and reported a total of 14 sites lost less than or equal to 2 mm of attachment. It should be noted that some sites may have lost less than 2 mm of attachment, however, we were unable to extract this information.

Finally, one study with 64 participants with a follow up of 144 months in SPC reported mean annual proportions of sites showing 2 mm attachment loss with respect to baseline PPD (Table 2) (Ramberg et al. 2001). The greatest mean proportion was consistently seen in the PPD≥6 mm category for the SRP group which was 7.5% (±6.4) between 12 and 36 months, 7.8% (±8.7) from 36-60 months and 2.9% (±8.2) between 60 and 156 months of SPC.

FQ-2

Two studies reported on the sites with CAL loss≥2 mm (Jenkins et al. 2000, Tonetti et al. 2012) and both trials reported no statistically significant difference between test and control groups (Appendix S11).

One controlled clinical trial (CCT) (Jenkins et al. 2000) assessed 17 patients (146 sites) in a coronal scaling (CS) group versus 14 patients (130 sites) in a subgingival scaling (SS) over a 12 month period. Participants whom previously had been treated for periodontitis and entered SPC, presented with at least 4 pockets of PPD ≥4 mm. The appropriate intervention was delivered at baseline, 3, 6 and 9 months. The authors reported 21 of these 'loser' sites (defined as CAL loss≥2 mm) in each group, and no statistically difference between groups was found. Initial PPD ≥6 mm demonstrated a greater proportion of sites that were 'loser' sites, 28.6%, compared to 11.6% of those with initial PPD 4-5.9 mm for the SS group. The corresponding proportions for the CS group were 20.5% (initial PPD≥6 mm) and 11.8% (initial PPD 4-5.9mm). The authors

concluded that the risk of attachment loss was greater if the initial PPD was 6mm or above, however this was only statistically significant for the SS group.

Tonetti et al. (2012) reported on 202 subjects in a multicentre RCT, comparing SRP and a single adjunctive 14% doxycycline gel application to SRP alone with a follow-up of 12 months. Participants had previously been treated for periodontitis and presented with at least four teeth with residual PPD ≥5 mm and a positive BOP. SPC was performed every 3 months for 1 year. A total of 15 participants (7.5%) experienced CAL loss≥2 mm (8 test, 7 controls). No statistically significant difference between groups were reported for any parameters at the 12 months.

3.5.3 Pockets of 5 mm or More with Bleeding on Probing

No studies reported specifically on the number of pockets of ≥5 mm with bleeding on probing during the SPC phase, but some reported on the proportion of sites within specific PPD categories. Additionally, for treatment of recurrence in SPC, the mean number of sites with PPD≥5 mm were reported without mention of bleeding on probing (Bogren et al. 2008, Tonetti et al. 2012).

3.5.4 Sites That Need/ Experience Retreatment

Kaldahl et al. (1996b) reported at total of 685 breakdown sites (461 from the SRP, Modified Widman Flap (MWF) and osseous recontouring groups) during the course of SPC that required re-treatment. From this, 5-12% of breakdown sites (experienced ≥3 mm attachment loss) which were subsequently re-treated, experienced further loss of attachment.

3.5.5 Oral Health Related Quality of Life (OHQoL)

The only study that reported on OHQoL was Cortellini et al. (2020). This study used the Italian translation of the Oral Health Impact Profile (OHIP)-14 questionnaire at baseline, 1, 5 and 10 years after treatment. One year after regenerative treatment (the first reassessment after APT), the mean OHIP-14 score was 6.6 (±2.4) and this was compared to a rehabilitated group (not relevant to this review). No data were reported at 10-years.

One study (Cortellini et al. 2017), reported recurrences that required retreatment. These recurrences occurred in all three treatment groups, MWF, modified papilla preservation technique (MPPT) with expanded-polytetrafluroethylene membrane (e-PTFE) and flap with e-PTFE. A total of 26 recurrences occurred in 20 years where sites of PPD≥5 mm at the 1-year reassessment, showed the highest frequency of recurrence that required re-intervention.

3.5.6 Health Economic Outcomes

Two studies (Cortellini et al. 2017, Cortellini et al. 2020) reported total cumulative costs for operative interventions. This cost calculation included actual cost of the procedures (using average fees from nine practices in Italy), all complications experienced which required re-treatment, and included tooth loss. Cortellini et al. (2020) reported (in graphical form) that the cumulative costs for a regenerative procedure over 10 years, amounted to a mean of just over €2500, however SPC appointments were not included in this calculation. The cumulative costs over a 20 year period (including 3 monthly SPC) ranged from a mean of €3090.98 (±210.66) to €3382 (±88.95), depending on the initial surgical therapy (Cortellini et al. 2017).

3.5.7 Other Patient Reported Outcomes (PRO)

One study (Kaldahl et al. 1996a) reported on the occurrence of periodontal abscesses in the context of the therapy type in APT, over the 84 month follow-up. Twenty-seven abscesses were reported, with 23 episodes (85%) occurring in the group originally treated by coronal scaling alone. Deep probing depths (≥7 mm) at the initial examination was associated with 17 abscesses (63%).

Masticatory function and aesthetics were assessed by Cortellini and co-workers (Cortellini et al. 2020). A 5-point Likert scale was utilised to assess changes from baseline to 10 years. The authors report that between the one and ten-year follow-up period, the proportion of participants with ‘no concern’ in regard to masticatory function remained stable. Those reporting, ‘some concern’ appears to increase over the 9 years of SPC (graphical information available only). A similar scale was used for assessing aesthetics, and once again, whilst those reporting ‘no concern’ appears to remain stable

between the one and ten-year follow-up, those reporting 'some concern' appears to increase over the follow-up.

Two studies reported on adverse events in the context of experimental treatment groups (Jenkins et al. 2000, Tonetti et al. 2012). Jenkins et al. (2000) reported no adverse events in relation to coronal and subgingival scaling. In contrast, Tonetti et al. (2012) reported that as 12 months 49 patients (75 adverse events) in the control group and 34 patients (56 adverse events) in the test group. The authors reported no difference in the incidence of adverse events was observed between the groups (a test of significance was not carried out).

3.6 Risk of Bias

FQ-1

All studies were assessed as prospective cohorts (SPC being the exposure) using the modified version of the NOS. Overall, most studies had a low risk of bias (Appendix S12), assessed as having five out of a possible six stars in regard to the selection and outcome domains. Two studies were found to have a moderate risk of bias, with four stars (Hou et al. 1997, Loesche et al. 2002), with one of these studies having a low score in the exposure/ outcome domain (Hou et al. 1997). When assessed by means according to domains of the NOS, it was found that 'selection' had an average score of 2.9 (SD ± 0.3), whilst the 'outcome/ exposure domain' showed an average 2.5 (SD ± 0.6).

FQ-2

Four RCTs were assessed using the Cochrane Risk of Bias Tool 2.0 (Appendix S13). Three studies were judged as being of, 'some concern' (Bogren et al. 2008, Lulic et al. 2009, Tonetti et al. 2012), whilst one study was deemed to be, 'high' risk (Killeen et al. 2018).

The Robins-I tool was used to assess the quality of one interventional non-randomised controlled trial (Jenkins et al. 2000) and one prospective cohort (Costa et al. 2015). Both studies were judged to be of 'serious' overall risk of bias (Appendix S14).

4. DISCUSSION

4.1 Key Findings

Findings of the meta-analyses indicated that the proportion of patients who experienced tooth loss was 9.6% (95% CI 5-14%) i.e. 10% of patients can expect to lose at least one tooth during SPC of at least 5 years duration. Subgroup analysis showed that the proportion of patients with regular 3 monthly SPC recall visits whom experienced tooth loss was 8.0% (95% CI 2-14%), compared with 11.9% (95% CI 5-19%) for the IRREG SPC group (p=0.161). A shorter length of follow-up (5-10 years) corresponded to an average of 8.2% (95% CI 3-13%), and as this time period increased (>10 years), the proportion also increased to 12.7% (95% CI 4-22%). Studies which could not be included in the meta-analyses reported a mean tooth loss per patient of 0-2.7 (±3.7), which was not greatly affected by the length of follow-up in SPC.

Patients who experienced at least one site of CAL loss≥2 mm was estimated to be 24.8% (95% CI 11-38%) i.e. 25% of patients can expect to have at least one site with progression of periodontitis by at least 2 mm during SPC of at least 5 years duration. According to the subgroup analyses, more patients who underwent 3 monthly SPC experienced CAL loss≥2 mm, which amounted to 30.2% (95% CI -2 – 63%), whilst the proportion of those in IRREG group SPC was 21.4% (95% CI 10-33%). The longer length of follow up of >10 years, led to a slightly higher proportion of patients with attachment loss of 26.3% (95% CI 8-45%) as compared to 22.1% (95% CI 5-39%) for the 5-10 yr group.

4.2 Agreements and Disagreements with Other Reviews

To our knowledge, this is the first systematic review assessing disease progression with the primary outcome of tooth loss, in the phase of SPC in the long term (> 5years).

The results of our review agree with a recent Cochrane review (Manresa et al. 2018) which reported on RCTs with a minimum of 12 months follow-up to determine the effects of maintenance care in the management of periodontitis. The authors found the quality of evidence to be low or very low and could not make conclusions on the merit of SPC

versus monitoring alone/irregular SPC. Furthermore, no conclusion could be drawn regarding the optimum frequency of SPC.

One recent systematic review (Sanz-Martin et al. 2019) similar to the present review, reported mean CAL loss ranging from ≤0.5 mm to >1 mm and proportion of sites showing CAL loss≥ 2mm ranging from 3-20% in their qualitative review. We were unable to compare the outcomes, as reporting of CAL loss in the current review was different and on a patient level. Tooth loss was reported at 1% based on one study only. One explanation for the differing results could be that Sanz-Martin et al. (2019) excluded regeneration studies, which formed a key part of the current review. Additionally, the present review only included studies with minimum 5 years specifically in the phase of SPC, rather than 5 years follow-up (which was often calculated before APT). Quality assessment also differed. The present review employed the modified version of the NOS to assess the SPC phase only, whereas the previous authors assessed studies based on the APT phase (thereby using the Cochrane collaboration tool for RCT and NOS for prospective cohorts). Their judgement was thus that most studies were at a high risk of bias, compared with this review which found that most studies were at low risk of bias.

4.2.1. Overall completeness and applicability of the evidence

This review intended to focus on patients diagnosed with stage IV periodontitis, however, the majority of studies were published prior to the most recent classification, with the exception of one (Cortellini et al. 2020), whereby the authors retrospectively classified patients as stage III-IV. No data could be extracted on what would specifically be considered stage IV periodontitis. In light of the fact that we have a lack of data on complexity factors such as numbers of teeth previously lost to periodontitis, masticatory dysfunction, bite collapse and/ or remaining teeth, it would be reasonable to assume that the majority of studies in this review probably represent stage III periodontitis patients. It is unclear to what extent complexity factors might influence disease recurrence in SPC, and thus our results might be generalised to include stage IV cases.

The limited number of studies included in this systematic review might seem surprising, however prospective long-term studies (> 5 years) in the periodontal literature are rare, with majority having a clear focus on the outcomes of APT with ≤12 months follow-up.

It is unclear if the data presented are representative of disease occurrence, recurrence or progression, furthermore, it is unclear if tooth loss was due to periodontitis alone. A number of studies did not present any information on reasons for tooth loss, thus the results presented in this review could be over-estimated. Although our subgroup analysis, showed that the proportion of patients who experienced CAL loss≥2 mm was greater for those in the 3M subgroup than the IRREG SPC subgroup, this difference was not statistically significant. Additionally, the disparity may be explained by a single outlier (Cortellini et al. 2017) whereby participants in this group presented with a greater number of residual PPD at the start of SPC and subsequently greater disease recurrence.

The studies in this systematic review were largely conducted in the university setting, with only a few conducted in private practice, some of which were from the same practice. Additionally, the meta-analyses included studies whereby regenerative procedures were part of APT, which limits the applicability of the evidence to all periodontal patients in general practice. The variability of SPC recall intervals and possible variety of operators however, may be more realistic of that which occurs in practice. This systematic review was also unable to inform on specialist versus non-specialist SPC in regard to disease progression/recurrence. A previous systematic review (Gaunt et al. 2008) reported that SPC delivered in specialist care represented a greater financial cost, but this was accompanied by greater periodontal stability (CAL) over a minimum follow-up period of 12 months.

There was an obvious lack of detail in regard to the description of SPC and the majority of studies provided no information on whom carried out the recall appointments. Use of the CONSORT – NPS extension (Leow et al. 2016) might help guide authors to describe the SPC intervention more completely even for non-randomised trials.

Studies which included PRO and health economic data were clearly lacking, therefore no conclusions could be made on the impact of disease recurrence in regard to these important outcomes from this review. However, health economic modelling of SPC has

demonstrated that it is cost-effective in developed economies when considering tooth loss or progression of CAL (Pennington et al. 2011). Furthermore, prevention of tooth loss in an aging population is a priority for long-term health and wellbeing (Tonetti et al. 2017). In relation to oral health-related quality of life (OHQoL) a recent pilot study has shown that after 32 years of SPC, OHQoL impacts are low. Interestingly, there were higher OHQoL impacts associated with 'insufficient' adherence to SPC compared with those with 'sufficient' adherence (Graetz et al. 2020).

Four studies specifically investigated treatment of recurrence in SPC, with only two being RCTs. Due to heterogeneity in terms of methodology and outcome reporting we were unable to answer FQ-2. Some of the included studies that addressed FQ-1 indicated that management of recurrence was left to the discretion of the operators, but usually were managed by further subgingival debridement. Success of this treatment modality in regard to resolution or halting progression of disease was not reported, although one study mentioned that, 'most' recurrent sites responded favourably to NST (Costa et al. 2015).

4.2.2. Overall Quality, Strength, and Consistency of the Evidence

The quality assessment judged the majority of included studies had a low risk of bias in regard to the SPC phase (FQ-1), with two studies found as having moderate risk. The meta-analysis highlighted heterogeneity for both tooth loss and CAL loss≥2 mm, which reflects the limited number of studies fulfilling the inclusion criteria for this systematic review. Type of initial therapy (regenerative or non-regenerative) was one factor that could explain some heterogeneity, however residual unexplained heterogeneity should be assumed, and results should be interpreted with caution. Studies included in the meta-analysis were predominantly of a regenerative nature. Split mouth studies were included in this review, and it should be acknowledged that there is an uncertain risk of contamination from one side/ quadrant to another. This, however, would be most relevant for studies assessing APT. The strength of the evidence to answer FQ-2 was weak, with two studies having a, 'serious' risk of bias (Robins-I tool), three studies of, 'some concern' and one study determined as having a, 'high' risk of bias (Cochrane Risk of Bias Tool 2.0). There was no clarity on which treatment modality (if any) was superior in the management of disease recurrence/ progression in SPC.

Finally, it should be recognised that studies included in this review were not originally designed for assessment of disease progression/recurrence and/or treatment of recurrence in SPC, thus the strength of conclusions from these studies is weak.

4.3 Strengths and Limitations of the Review

In order to minimise the risk of bias in the review process, this protocol was submitted *a priori* to PROSPERO. Furthermore, screening, study eligibility, data abstraction and quality assessment were all conducted in duplicate and independently.

This systematic review is the first to comprehensively look at disease progression/ recurrence in SPC, incorporating all forms of treatment in APT, over a minimum of 5 years in maintenance. Additionally, it is the first to assess methods of managing disease progression/ recurrence of patients in an established SPC programme. We incorporated a sensitive search strategy in multiple electronic databases in order to detect a broad range of studies. Other strengths were the quality assurance including duplicate, independent study screening and data extraction.

A number of studies described a significant number of drop-outs over the follow up period, and in order not to underestimate the prevalence of tooth loss and CAL loss≥2 mm we chose to carry out a per protocol meta-analyses, however for comparison and thoroughness, an ITT analysis was also included for tooth loss.

A number of limitations could be identified which might bias the outcomes of this systematic review.

Publication bias is an important problem in evidence-based Medicine, and this may lead to selection bias in systematic reviews. In the present review, some publications following the screening of titles and abstracts could not be obtained in full-text and clarification on studies from authors could not be followed up. We were also limited to

publications in the English language, which means that relevant studies could have been missed.

Some post-hoc changes were made to the original protocol. We added case-series to the exclusion criteria, and a distinction was also made as to what we defined as a case-series versus prospective cohort. Additionally, a modified version of the NOS needed to be implemented to adjust for the studies included in the review.

One post-hoc analysis was included based on the data collected. This was subgrouping according to SPC recall intervals and was conducted as it became clear that a number of studies had quite variable or unmonitored SPC visits.

4.4 Implications for Practice and Policy

Most patients enrolled in SPC following successful treatment of periodontitis should not expect to experience tooth loss, which, considering the severity of disease (stage III or IV periodontitis) is highly encouraging. However, 25% of patients are likely to experience further CAL loss. It is unclear from the data whether the CAL loss represents periodontitis progression or gingival recession in shallow pockets. However, in some studies (Bogren et al. 2008, Costa et al. 2015, Cortellini et al. 2017), CAL loss was noted as an increase in PPD at some sites, suggesting disease progression. These findings, together with other evidence discussed in this review, highlight that SPC is an important element in the long-term management of stage III and IV periodontitis.

Evidence external to this review indicates that SPC is cost-effective in developed economies (Pennington et al. 2011, Schwendicke et al. 2020) and that prevention of tooth loss is important in ageing populations (Tonetti et al. 2017).

Although SPC is poorly described in the literature, the common elements in studies suggest that it should include repeated; risk assessment, health behaviour motivation, tailored oral hygiene coaching, professional mechanical plaque removal and targeted subgingival debridement appropriate for each patient (Rosling et al. 2001). The recently published 'Clinical Practice Guideline' from the recent European Federation of Periodontology (Sanz et al. 2020) supports inclusion of these elements also. Individual

needs of each patient should be considered when deciding on the frequency of SPC, and, until the influence of risk factors is better understood, this is likely to be no longer than 3-6 monthly for stage III-IV periodontitis patients. Whilst there was no evidence of a difference in tooth loss between groups receiving 3 monthly and less regular SPC, it is important to remember that these were not randomised controlled trials and were therefore at higher risk of bias. A lack of randomised evidence was also found in another systematic review (Manresa et al. 2018).

4.5 Implications for Further Research

There is a clear need for high quality trials focussed on SPC, with particular attention to SPC recall intervals, and documenting and treating disease progression/ recurrence. SPC should be carefully described in detail including who delivered it and the components of care using the CONSORT-NPE as a guide, even for non-randomised studies. The demographics of the population entering SPC should be clearly described, particularly with reference to risk factors of smoking and diabetes. Information on tailoring procedures in each SPC visit and recall intervals would be highly valued.

In order to increase the clinical relevance of studies, it would be ideal to report outcomes such as tooth loss or CAL loss at a patient level, in addition to mean values. Patient reported outcomes and costs of treatment would also be important and essential aspects of a clinical trial.

5. CONCLUSIONS

Within the limitations of this study, we have found that the mean prevalence of tooth loss in patients in SPC for 5 years or more is less than 10% of patients, with a tendency for greater prevalence with time. Regular SPC appointments (3 monthly) appears to be important for reduction of the prevalence of tooth loss.

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