# Studies on the Prevention of Periodontal Diseases

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*To my mother and father*

*Ilse and Bertil Bogren*

# Contents

# Abstract

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Dental plaque contains bacteria that colonize the subgingival area and causes periodontal diseases. Effective plaque removal is therefore a key issue in the prevention of the development/progression of periodontal diseases.

The main objective of the present series of investigations was to evaluate clinical and microbiological changes/effects of various prevention means in two subject samples with diverse experience of destructive periodontal disease.

160 adult subjects without clinical signs of destructive periodontal disease and 128 patients previously treated for periodontitis and involved in regular maintenance therapy were recruited. The individuals in the two subject samples received professional prophylaxis/supportive periodontal therapy every 6 months and were followed over a 3-year period. All participants were randomized to use either powered toothbrush combined with a triclosan-containing dentifrice or manual toothbrush and a standard fluoride dentifrice. The patients previously treated for periodontitis were furthermore randomly assigned to receive i) mechanical debridement plus locally applied doxycycline or ii) mechanical debridement alone, in sites with PPD ≥5 mm. Full mouth clinical registrations of plaque, bleeding on probing (BoP), probing pocket depth (PPD) and relative attachment level (RAL) were performed at baseline, 3 months 1, 2 and 3 years. At each examination interval subgingival plaque samples were taken at each tooth for analysis of the prevalence of 40 different bacterial species.

The subjects without destructive periodontal disease improved their clinical periodontal conditions over the 3 years with a significant reduction in BoP score and in PPD. This improvement was accompanied by a shift in the subgingival microflora to a more host-compatible microbiota. There were no differences in these respects between the two home-care programs.

The patients with a history of destructive periodontal disease showed significant reductions in BoP, PPD, and in mean counts of various bacterial species between baseline and 3 years while RAL remained unchanged. No significant differences were found in clinical or microbiological variables between the two home-care procedures. Short-term beneficial effects on clinical parameters were demonstrated with the adjunctive use of locally delivered doxycycline. Repeated application of the drug once annually had no long-term clinical or microbiological effects beyond those observed by subgingival mechanical debridement alone in this group of patients.

**Key words:** dentifrices, doxycycline, gingivitis, microbiology, periodontitis, prevention, randomized controlled trial, toothbrushing, triclosan

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# Preface

The present thesis is based on the following studies, which will be referred to in the text by their Roman numerals:

**I.** Bogren A, Teles RP, Torresyap G, Haffajee AD, Socransky SS, Lindhe J, Wennström JL. (2007) A three-year prospective study of adult subjects with gingivitis. I. Clinical periodontal parameters. *Journal of Clinical Periodontology* 34:1-6.

**II.** Teles RP, Bogren A, Patel M, Wennström JL, Socransky SS, Haffajee AD. (2007) A three-year prospective study of adult subjects with gingivitis. II. Microbiological parameters. *Journal of Clinical Periodontology* 34:7-17.

**III.** Bogren A, Teles RP, Torresyap G, Haffajee AD, Socransky SS, Wennström JL. (2007) Clinical and microbiologic changes associated with the combined use of a powered toothbrush and a triclosan/copolymer dentifrice: A 3-year prospective study. *Journal of Periodontology* 78:1708-1717.

**IV.** Bogren A, Teles RP, Torresyap G, Haffajee AD, Socransky SS, Jönsson K, Wennström JL. (2008) Long-term effect of the combined use of powered toothbrush and triclosan dentifrice in periodontal maintenance patients. *Journal of Clinical Periodontology* (Accepted for publication).

**V.** Bogren A, Teles RP, Torresyap G, Haffajee AD, Socransky SS, Wennström JL. (2008) Locally delivered doxycycline during supportive periodontal therapy: A 3-year study. *Journal of Periodontology* (Accepted for publication).

# Abbreviations

BL = baseline
BoP = bleeding on probing
CAL = clinical attachment level
CCT = controlled clinical trial
CE = clinical examination
CT = clinical trial
DF = dentifrice
GI = gingival index
IDC = interdental cleaning with floss/toothpicks/interdental brushes
LOA = loss of clinical attachment
NaF = sodium fluoride
NS = non significant
MT = manual toothbrush
OH = oral hygiene
OHI = oral hygiene instructions
PAL = probing attachment level
PI = plaque index
PPD = probing pocket depth
PT = powered toothbrush
RAL = relative attachment level
RCT = randomized controlled trial
ROA = rotation oscillation action
SPT = supportive periodontal therapy
SRP = scaling and root planing

# Introduction

This thesis is a report of prospective clinical studies on the prevention of periodontal diseases in adults. The investigations were performed in two different subject samples with diverse experience of destructive periodontal disease. The results of the trials were based on clinical and microbiological examinations of the subjects over a 3-year period.

## Background

Periodontal diseases involve pathologic processes affecting the tissues surrounding the teeth (gingiva, periodontal ligament and alveolar bone) and most forms are associated with dental plaque.

Gingivitis is clinically characterized by signs of inflammation in the gingiva, e.g. gingival redness, swelling and bleeding on gentle probing. There is no loss of connective tissues attachment or supporting alveolar bone. Dental plaque accumulation is a direct cause of gingivitis (Löe et al. 1965, Theilade et al. 1966, Lindhe & Rylander 1975, Brecx et al. 1987). In the classical study "Experimental gingivitis in man", Löe and coworkers (1965) demonstrated that after oral hygiene procedures were discontinued and dental plaque allowed accumulating, gingivitis developed within 3 weeks. Furthermore, the clinical signs of gingival inflammation were resolved within a few days after professional plaque removal and re-establishment of proper oral hygiene.

Plaque-induced gingivitis is a reversible form of periodontal disease, but left untreated it might progress to periodontitis, i.e. in addition to gingival inflammation, periodontal pocketing, attachment loss and alveolar bone loss (Löe & Morrison 1986, Lindhe et al. 1973, 1975, Kornman et al. 1997, Schätzle et al. 2003, 2004). The expression of periodontitis is due to interactions between various bacterial, host and environmental factors (Page & Kornman 1997). Exactly why and in which individuals the shift from gingivitis to periodontitis occurs, is at present not known. The progression of periodontitis might be prevented by treatment means directed towards infection control but the arisen injuries, loss of the attachment and alveolar bone, are mainly irreversible.

*Prevalence*

The prevalence of gingivitis and periodontitis in adults is relatively high. Now and then during a lifetime "all" individuals demonstrate clinical signs of gingival inflammation. It was estimated by Albandar (2002) that more than 50% of the population in the USA exhibited "gingivitis" (gingival bleeding), and in a recent

epidemiological study in a Swedish adult population on average 16% of the existing tooth sites showed gingivitis (Hugoson et al. 2005b). Regarding the prevalence of periodontitis, cross-sectional studies revealed a prevalence of about 40% in populations in the USA and Sweden and that the extent of the disease increased with age (Brown et al. 1989, Hugoson et al. 1998). However, severe forms of periodontal disease with a generalized pattern were shown to affect only a minority of individuals, about 10% (Hugoson & Jordan 1982, Brown et al. 1989, Hugoson et al. 1998, Albandar 2002, Sheiham & Netuveli 2002).

*Clinical diagnostic procedures*

The presence or absence of bleeding on probing (BoP) is aimed at describing the inflammatory condition of the gingival tissues. The probing force applied in the registration of BoP is crucial for the bleeding tendency, with increased bleeding when increased probing force is used (van der Velden 1980). When using a standard periodontal probe (probe tip diameter of 0.4-0.5 mm) the force applied is suggested not to exceed 0.25 N (Lang et al. 1991).

Gingival units that consistently bleed on probing have a higher risk for attachment loss compared with sites showing only occasional or no bleeding (Lang et al. 1986, Schätzle et al. 2003). Evidence suggests that if a site consistently bleeds on probing the risk to loose ≥2 mm of clinical attachment over a 2-year period is about 30% (Lang et al. 1986). Thus, absence of BoP was suggested to be a good predictor of periodontal stability (Lang et al. 1990).

Periodontal probing is also employed to measure probing pocket depth (PPD) and clinical attachment level (CAL) as means to diagnose presence and/or progression of destructive periodontal disease. However, in the interpretation of the probing measurements several factors have to be considered. When gingival inflammation is present there is an overestimation of the "true" pocket depth because the probe penetrates the base of the junctional epithelium (Listgarten et al. 1976, 1980). On the other hand, probing in a non-bleeding site might result in an underestimation since healthy tissues have greater resistance to the probing. However, van der Velden (1982) demonstrated that the tip of the probe is located more accurately at the attachment level in non-bleeding sites than in sites with bleeding. Besides the inflammatory status of the gingival tissues the diameter of the probe and the probing force used in the PPD/CAL registration procedure is an important issue for the accuracy as well as for the reproducibility of the measurements (van der Velden 1979, Mombelli et al. 2005).

Regarding PPD, a residual PPD of ≥5 mm has a diagnostic predictability of 28% for future (42 months) clinical attachment loss ≥1.5 mm, while PPD of ≥7 mm has a predictability of 50% (Claffey et al. 1990).

*Microbiological diagnostic procedures*

Microbial analysis has been suggested to be used in the diagnostic phase at the end of active treatment as well as in the treatment of persistent periodontal/peri-implant infections (van Winkelhoff & Winkel 2005). For the analysis of subgingival plaque, samples are collected primarily by use of curettes or paper points. The two sampling procedures differ in that the curette sampling method collects plaque from the entire biofilm while the use of paper points mostly samples from the outer subgingival plaque layers.

There are several different methods available for analyzing subgingival plaque samples. By darkfield microscopy classification of microorganisms into morphological categories can be performed; coccoid, motile rods, spirochetes and other cells (Listgarten & Helldén 1978). With culturing technique it is possible to detect various species in plaque samples. However, limitations of this technique include inability to detect low levels of microorganisms, inability or difficulty in growing several bacterial species, high costs and labor intensivity.

A method allowing the possibility of studying large numbers of bacterial species in a high quantity of samples containing complex mixtures of microorganisms is the so-called checkerboard DNA-DNA hybridization technique (Fig. 1.) (Socransky et al. 1994, 2004). With this technique it was demonstrated that bacterial species in subgingival plaque samples are closely related to each other and ordered in 5 major consistently observed complexes (Socransky et al. 1998, see Fig. 2) and that there are relationships and microbial succession patterns among the different microbial complexes. It was suggested by Socransky and coworkers (1998) that *Actinomyces* species and *Streptococci* are early colonizers followed by *Capnocytophag*a and *E. corrodens*. It was further suggested that the purple complex connects to the orange complex and that the members of the so-called "red complex" (*P. gingivalis, T. forsythia, T. denticola*), with a very strong relationship with pocket depth, seldom are found in the absence of members of the orange complex.

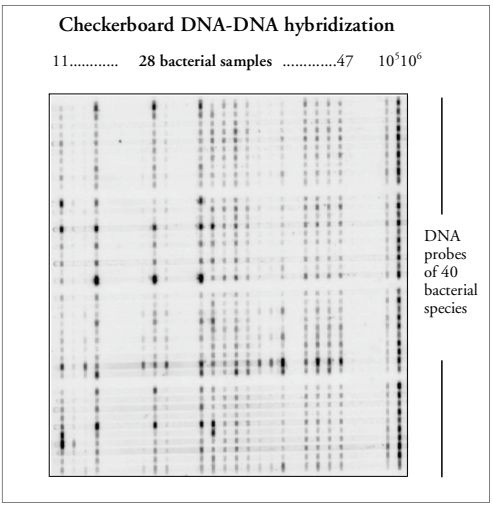
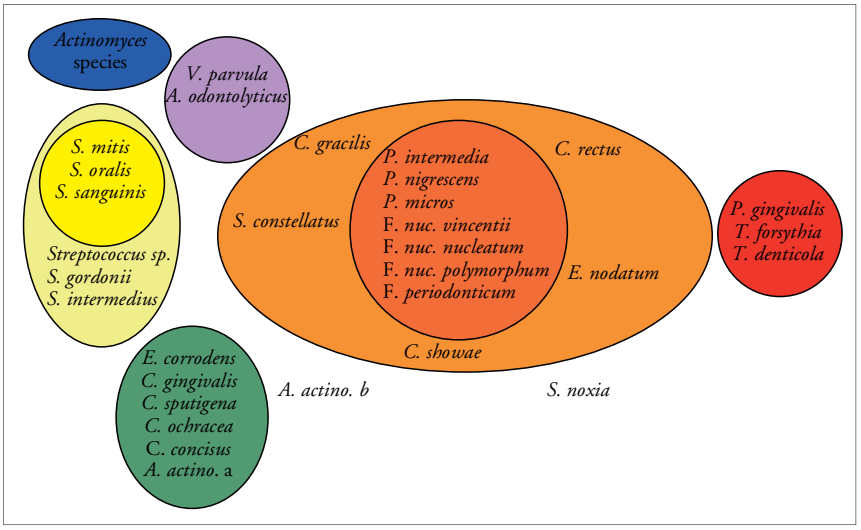



*Fig. 1.* Example of a checkerboard DNA–DNA hybridization to detect 40 bacterial species in 28 subgingival plaque samples from a single patient. The vertical lanes are the plaque samples numbered from 11 (right maxillary central incisor) to 47 (right mandibular second molar). The two vertical lanes on the right are standards containing either $10^5$ or $10^6$ cells of each test species. The horizontal lanes contained the indicated DNA probes. A signal at the intersection of the vertical and horizontal lanes indicates the presence of a species. The intensity of the signal is related to the number of organisms of that species in the sample. (Courtesy of Dr A. Haffajee)

*Fig. 2.* Diagrammatic representation of the relationship of species (updated *B. forsythus* to *T. forsythia*) within microbial complexes and between the microbial complexes (Socransky et al. 1998) (Reprinted with the permission from *Journal of Clinical Periodontology*)



The checkerboard DNA-DNA hybridization method has been extensively used in studies that examined composition of dental plaque in healthy and diseased sites/subjects as well as in longitudinal studies evaluating changes in plaque composition after periodontal therapy. The advantages of this method are that quantitative microbiological data can be provided and that the problem of the culturing technique with its difficulties in growing certain bacteria or detecting uncultivable species is not valid. Moreover, the method is regarded as rapid, sensitive and relatively inexpensive compared with e.g. the culturing technique. However, there are limitations with this method since only species for which DNA probes have been prepared can be detected.

*Clinical and microbiological characteristics of periodontally healthy and diseased subjects*

"Periodontally healthy or minimally diseased individuals" are commonly described in the literature as subjects with less than 20% of the gingival sites with BoP, no or only very few sites with PPD ≥5 mm and absence of interproximal attachment loss. Subgingival plaque samples from such subjects are characterized by significantly lower total bacterial counts, higher proportion of *Actinomyces* species and lower proportion of red and orange complex species compared with periodontitis subjects (Fig. 3) (Yang et al. 1994, Socransky et al. 1998, Ximénez-Fyvie et al. 2000).

*Prevention of periodontal diseases*

In medicine, prevention is divided into three forms; i) primary prevention, aimed at preventing the occurrence of a disease, ii) secondary prevention, aimed at preventing recurrence and/or stopping further progression of a disease and iii) tertiary prevention, aimed at the restoration of maximal function, minimization of the negative effects of disease and prevention of disease-related complications (Nationalencyklopedin, Dictionary).

Several rationales exist for periodontal disease prevention. The ultimate effect of destructive periodontal disease is tooth loss, which might lead to functional as well as esthetical problems for the individual. Loss of supporting periodontal tissues (without tooth loss) might also lead to functional/esthetical problems as a consequence of e.g. mobile tooth, orally exposed root surfaces and "black interproximal triangles". Furthermore, the loss of teeth and/or supporting tissues might require prosthetic therapy that is associated with high financial burden for the individual and for the insurance systems. Another important rationale for the prevention of periodontal diseases is the suggested association between chronic

periodontitis and systemic diseases, such as cardiovascular disease and diabetes (Paquette et al. 2007, Mealey & Ocampo 2007).

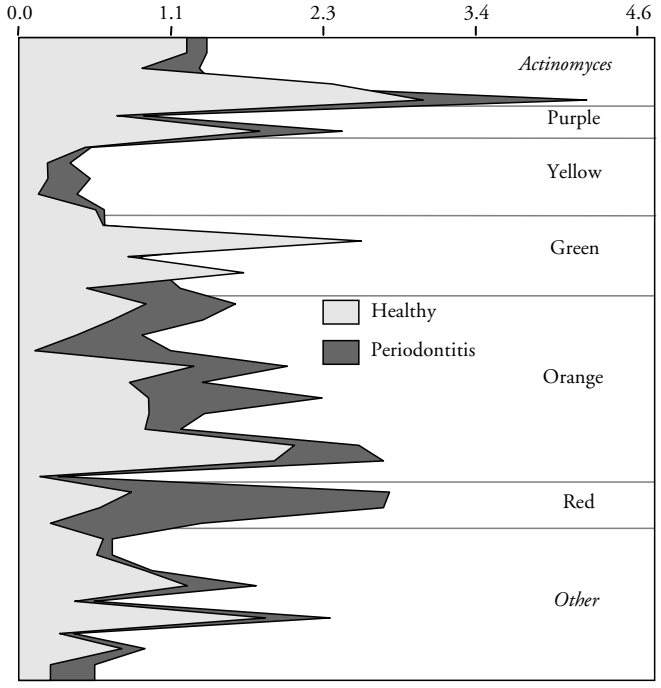



*Fig. 3.* Mean counts (x$10^5$) for 40 bacterial species in subgingival plaque samples from periodontally healthy and chronic periodontitis subjects (Courtesy of Dr A. Haffajee)

Primary prevention of periodontal diseases is targeted periodontally healthy individuals. Two methods that often are used in primary prevention of periodontal diseases are; i) personal oral hygiene measures including toothbrushing, interproximal cleaning, the use of dentifrices and mouthrinses, and ii) professional procedures (recalls with professional tooth cleaning and reinforcement of oral hygiene procedures). Clinical studies have demonstrated that the use of these methods are important for the prevention of periodontal diseases in children, adolescents as well as in adults (Lövdal et al. 1961, Soumi et al. 1971, Axelsson & Lindhe 1977, 1978, 1981a, Albandar et al. 1994, Hugoson et al. 2007).

Secondary prevention of periodontal diseases is directed to patients treated for periodontitis. Supportive periodontal therapy (SPT) includes recall at certain time intervals for re-examination, debridement of periodontal sites with clinical signs of pathology, tooth polishing, as well as reinforcement of self-performed oral hygiene procedures (Cohen 2003), is an example of secondary prevention of

periodontitis. It has been shown that SPT is of great importance in achieving and maintaining stable periodontal conditions in periodontitis susceptible patients (Axelsson & Lindhe 1981b, Ramfjord et al. 1982, Lindhe & Nyman 1984, Axelsson et al. 2004).

## Powered toothbrushes

Toothbrushing is probably the most frequently used measure in self-performed plaque removal procedures, and most individuals in industrialized countries brush their teeth once or twice daily as a part of their daily hygiene routine (Lang et al. 1994, Sheiham & Netuveli 2002, Hugoson et al. 2005a). However, the plaque removal by use of a manual toothbrush has been demonstrated to be insufficiently effective (van der Weijden & Hioe 2005).

In attempts to improve the effectiveness of plaque removal by toothbrushes, powered toothbrushes were developed and introduced into the market in the 1960s. Since then there has been a continuous development in the design of the toothbrushes e.g. standard "side to side" powered toothbrushes, rotary, counter oscillation, ultrasonic, ionic and powered toothbrushes with a rotation-oscillation action (ROA).

The ROA powered toothbrushes were introduced in the beginning of the 1990s and have been extensively evaluated (see literature overview Table 1). Van der Weijden and coworkers (1993a, b) tested the efficacy in plaque removal of this new design of powered toothbrush. Even though the efficacy of plaque removal increased with brushing time for all tested toothbrushes, the ROA powered toothbrushes removed more plaque than manual toothbrushes and other powered toothbrushes when less than 6 min brushing time was used. These studies were, however, "experimental plaque accumulation studies" in selected groups of subjects. The efficacy of ROA powered toothbrushes in plaque removal and possible effect on gingival health was further evaluated in different groups of patients in more "real-life" designed studies (Stoltze & Bay 1994, van der Weijden et al. 1994, Ainamo et al. 1997, Haffajee et al. 2001b, Dentino et al. 2002, McCracken et al. 2004). The main findings from these studies are presented in Table 1. In the interpretation and comparison of the findings of these studies differences in characteristics of the study samples, study-length, OH assessments, selection of plaque/gingivitis indices and study design have to be considered. For example, using only students as participants in "real-life" studies might not accurately reflect the outcome in the general population, and to make reasonable conclusions about "true" long-term clinical effect of powered toothbrushes the study period might have to be longer than 1-year.

Based on data obtained from systematic reviews, it was concluded that the use of ROA powered toothbrushes have superior effects compared with the use of manual toothbrush in the reduction of plaque and gingivitis (Sicilia et al. 2002, Deery et al. 2004, Robinson et al. 2006). The magnitude of the difference in the

reduction of plaque and gingivitis between the two types of toothbrushes was 11% and 6% respectively in the short-term and 7% and 17% in the long-term (>3 months) (Deery et al. 2004). Furthermore, it was concluded that no design of powered toothbrush other than ROA was found to be superior in these respects compared with manual toothbrushes.

*Table 1.* Overview of selected publications on ROA powered toothbrushes

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **van der Weijden et al. 1993 (a)** | CCT, split-mouth, single-blind<br>Short-term<br>PI<br>Six sites/tooth, full mouth<br>3 experiments (A, B, C)<br>A=professional toothbrushing<br>B=Panelist toothbrushing<br>C=Panelist toothbrushing after OHI | Adults,<br>60 dental students<br>3 groups (I, II, III)<br>(6 dropouts experiment C) | (I) MT vs PT<br>(II) MT vs ROA PT<br>(III) PT vs ROA PT<br>No OH 24 h before visit | Experiment A;<br>PT & ROA PT improved PI better compared to manual (~86% vs ~78%) ($p$ <0.01) and<br>ROA PT better than PT (~87% vs ~84%) ($p$ <0.01)<br>Experiment B;<br>No difference in efficacy<br>Experiment C;<br>ROA PT better than PT (~84% vs ~78%), and than manual (~83% vs ~78%) |
| **van der Weijden et al. 1993 (b)** | CT, split-mouth 4 quadrants, single-blind<br>PI<br>Full mouth score, 6 sites/tooth<br>5 "timer" experiments<br>CE after 24 h plaque accumulation | Adults<br>20 dental students/junior staff (no dropouts)<br>4 groups (I, II, III, IV) | (I) MT<br>(II) PT 1<br>(III) PT 2<br>(IV) ROA PT | Efficacy of plaque removal improved with the time used for all groups<br>Major part of improvement at 30 sec/quadrant<br>ROA PT/PT 2 better at all times than PT 1/MT |
| **Stoltze & Bay 1994** | RCT, parallel, single-blind<br>6 weeks<br>PI, GI<br>CE at BL, 1, 2, 6 weeks<br>Full mouth score, 6 sites/tooth | Adults<br>40 medical students, 20 test/20 control (2 control dropouts)<br>PI >1, GI >1 | ROA PT (test)<br>MT (control)<br>OH 2x a day, 2 min.<br>No IDC<br>No OHI | PI >1 improved for both groups over time ($p$ <0.05)<br>GI >1 improved only for ROA PT over time ($p$ <0.05)<br>Significant superior improvements in PI/GI at 2 and 6 weeks for PT ($p$ <0.05) |
| **van der Weijden et al. 1994** | RCT, parallel, single-blind<br>8 months<br>PI, GI, BoP<br>CE at baseline, 1, 2, 5, 8 months<br>"Half-mouth" score (1st/3rd or 2nd/4th quadrant), 4 sites/tooth | Adults<br>87 students, 44 test/43 control (2 test/8 control dropouts)<br>BoP ≥35%<br>No PPD ≥5mm or LOA ≥2mm | ROA PT (test)<br>MT (control)<br>OH 2 min.<br>IDC habits as usual<br>OHI only in toothbrushing at 1, 2, 5 months | All clinical variables improved over time for both groups<br>Significant superior improvements in PI/BoP after 5 months and in GI at 8 months for ROA PT ($p$ <0.05) |
| **Ainamo et al. 1997** | RCT, parallel, single-blind<br>12 months<br>PI, BoP<br>CE at baseline, 3, 6, 12 months | Adults, mean age ~38 years<br>111 office workers without dental training<br>55 test/56 control (1 test dropout) | ROA PT (test)<br>MT (control)<br>OH 2 min. 2x a day<br>IDC habits as usual<br>SPT incl. OHI at | PI and BoP improved for both groups over time<br>NS differences in PI between groups at all time points<br>ROA PT significantly |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | "Half-mouth" score (1st and 3rd quadrant), plaque bucc/ling, BoP 6 sites/tooth | BoP ≥30% | baseline | superior to MT in BoP at 6, 12 months ($p$ =0.01) |
| **Haffajee et al. 2001b** | RCT, parallel, single-blind<br>6 months<br>PI, GI, BoP, PPD, CAL<br>CE at baseline, 3, 6 months<br>Full-mouth score, 6 sites/tooth | Adults, mean age ~48 years<br>52 periodontal maintenance patients, 26 test/26 control (4 test dropouts)<br>≥20 teeth, >10% sites with PPD ≥4 mm, >10% sites with CAL >4 mm | ROA PT (test)<br>MT (control)<br>OH 2x a day<br>IDC habits as usual<br>SPT at BL, 3 months | PI, BoP, PPD improved for both groups over time ($p$ <0.05)<br>GI, CAL improved over time for ROA PT only ($p$ <0.05)<br>NS differences between groups at all time points for all clinical parameters |
| **Dentino et al. 2002** | RCT, parallel,<br>6 months<br>PI, GI, BoP<br>CE at BL, 3, 6 months<br>Full-mouth score, 6 sites/tooth GI/BoP, 4 sites/tooth PI | Adults, mean age ~32 years<br>172 subjects without previous experience<br>PT, 86 test/86 control (10 test/5 control dropouts)<br>BoP ≥20% | ROA PT (test)<br>MT (control)<br>OH 2 min. 2x a day<br>No IDC<br>OHI written | PI, GI, BoP improved for both groups over time ($p$ <0.05)<br>Significant superior effect in PI of ROA PT<br>NS differences between groups in GI/BoP at all time points |
| **Sicilia et al. 2002** | Systematic review, RCT short- and long-term studies<br>Search to June 2001<br>Primary outcome variable-reduction in gingivitis | 21 articles, 15 short-term, 6 long-term<br>Gingivitis or periodontitis subjects >15 years | PT (test)<br>MT (control)<br>4 methodological models<br>i) "Over-the-counter"<br>ii) "OHI"<br>iii) "Prophylaxis + OHI"<br>iv) "SPT" | i) 2 short-term studies significant better result for PT NS differences between PT & MT in 2/4 studies<br>ii) 4 short-term studies significant better result for PT<br>NS differences between PT & MT for 4/8<br>iii) 3 short-term studies NS differences between PT & MT, 2 long-term significant better result for PT<br>iv) 3/3 long-term studies significant better result for PT |
| **Deery et al. 2004** | Systematic review with meta-analysis<br>Primary outcome-level of plaque and/or gingivitis | RCT short- and long-term studies (28 days-3 months/ >3 months)<br>No age limit for subjects<br>No split-mouth designed studies<br>Search to August 2002<br>29 articles, 10 long-term | PT (test)<br>MT (control)<br>6 PT models (different mechanical movement) | Significant improvements in plaque & gingivitis for both short- and long-term in favor of ROA PT versus MT ($p$ <0.05)<br>PI was reduced 11% and 7% and gingivitis 6 % and 17% more for the short- and long-term periods respectively<br>No other PT designs were superior to MT |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **McCracken et al. 2004** | RCT, parallel,<br>16 months<br>CE; PI at BL, 1, 2, 3, 4, 5, 6, 8, 10, 16 months<br>BoP, PPD at BL, 3, 6, 10, 16 months<br>Full-mouth score, 6 sites/tooth<br>Primary outcome-PI<br>Secondary-BoP, PPD | Adults, mean age ~49 years<br>40 periodontitis subjects<br>No previous PT,<br>20 test/20 control (4 test/4 control dropouts)<br>≥10 sites with PPD ≥5 mm | ROA PT (test)<br>MT (control)<br>OH 2 min. 2x a day<br>IDC<br>SPT incl. OHI at baseline, 3, 6, 10, 16 months | Significant improvements in PI, BoP, PPD over time for both groups ($p$ <0.001)<br>NS differences between the two groups in PI, PPD at all time points<br>Significant difference in BoP in favor of MT at 16 months |
| **Robinson et al. 2006** | Systematic review<br>Primary outcome-level of plaque and/or gingivitis | RCT short- and long-term studies (28 days-3 months/ >3 months)<br>No age limit for subjects<br>No split-mouth designed studies<br>Search to July 2004<br>42 articles | PT (test)<br>MT (control)<br>7 PT models (different mechanical movement) | ROA PT significantly improved plaque score (11%) & gingivitis (6%) in short-term and gingivitis (17%) in long-term compared to MT<br>No other PT designs were superior to MT |

## Triclosan dentifrices

Dentifrice in combination with toothbrushing might today be considered as the fundamental part of the oral hygiene procedure for most individuals in industrialized countries. Besides the general well being of using a dentifrice the purpose is to facilitate plaque removal and, by incorporating different agents, obtain therapeutic or preventive effects. The majority of the so-called standard/regular dentifrices available on the market contain the anti-caries agent fluoride as one component. Fluoride incorporated in dentifrice was introduced in the industrialized countries about 40 years ago and is today the most common vehicle used for delivering fluoride to the oral cavity (Twetman et al. 2003). Besides the fluoride component, standard dentifrices contain abrasives, surfactant and flavor for mouth freshness.

To prevent biofilm formation and development of gingivitis various anti-plaque agents such as chlorhexidine, enzymes, herbal extracts, metal salts and triclosan have been incorporated in dentifrices. Since dentifrice is regarded as a long-term use dental product there are, however, important considerations that have to be taken into account when incorporating an antibacterial agent into dentifrices. The antibacterial agent should i) not disrupt the natural balance of the oral microflora, ii) not lead to colonization by exogenous organisms and iii) not lead to the development of microbial resistance (Marsh 1992).

Triclosan acts as a broad-spectrum biocide causing disruption of bacterial cells and has been used safely as an antibacterial agent in different consumer products such as soap and deodorants for more than 30 years. Triclosan is maybe the most widely used and investigated antimicrobial agent in dentifrices and is regarded as a suitable antimicrobial agent due to its i) broad-spectrum activity on oral G+ and G- bacteria and ii) compatibility with other dentifrice ingredients (Panagakos et al. 2005). Evidence shows that triclosan incorporated in dentifrices does not result in shifts in the oral microflora favoring the growth of either opportunistic or pathogenic bacterial species, or promote the acquisition of microbial resistance (Zambon et al. 1990, Walker et al. 1994, Zambon et al. 1995, Cullinan 2003a). Furthermore, in addition to the anti-bacterial effect a “direct” anti-inflammatory effect of triclosan has been suggested (Gaffar et al. 1995).

To improve the “anti-plaque” activity of triclosan in a dentifrice it is combined either with i) another antimicrobial agent such as zinc citrate or ii) a co-polymer (polyvinylmethyl ether and maleic acid-PVM/MA).

The combination of triclosan and PVM/MA copolymer in dentifrices increases the oral retention of triclosan with greater uptake to enamel and epithelial cells and is more effective in reducing dental plaque formation compared with triclosan alone (Gaffar et al. 1990). The majority of the studies that have investigated the effect of triclosan/copolymer dentifrice on periodontal variables show positive results, however there are also studies with conflicting results. An overview of literature dealing with the clinical effects of triclosan/copolymer dentifrice is described in Table 2.

In a group of relatively young adults having moderate plaque and gingivitis scores the effect of triclosan/copolymer dentifrice on existing plaque and gingivitis was investigated (Lindhe et al. 1993). The individuals using the triclosan dentifrice reduced their plaque and gingivitis scores superior to what was accomplished with the standard dentifrice. However, the magnitude of differences in PI and GI at the final examination was rather modest.

In a study sample that was considered to represent a normal adult population, the long-term effect (5 years) of triclosan/copolymer dentifrice on the progression of periodontal disease was investigated (Cullinan et al. 2003b). The 504 subjects included were classified according to their disease status at baseline; <4 sites with PPD ≥3.5 mm or ≥4 sites with PPD ≥3.5 mm. The results demonstrated that triclosan dentifrice had no superior effect on the loss of attachment above that obtained by the use of a regular dentifrice. However, in sub-analyses of the interproximal sites showing PPD ≥3.5 mm or loss of attachment ≥2 mm at baseline, the use of the triclosan dentifrice reduced the number of sites with deepened pockets at the follow-up examinations compared with the subjects that used the placebo dentifrice. Based on this finding it was suggested that long-term use of triclosan dentifrice might slow down the progression of periodontal disease in subjects with existing disease. It should be pointed out, however, that the difference amounted only to 10% and 20% fewer pockets in the triclosan group that at baseline had 5 or 10 pockets respectively.

Rosling et al. (1997b) investigated the effect of a triclosan/copolymer dentifrice on periodontal parameters in periodontitis susceptible individuals that had been on maintenance for 3-5 years. The patients were randomly assigned to use either triclosan/copolymer dentifrice or a placebo dentifrice and were recalled every 3$^{rd}$ month for reinforcement of the oral hygiene. No subgingival instrumentation was performed at any of the recalls during the 3-year study period. It was demonstrated that “optimal” supragingival plaque control failed to prevent recurrence of destructive periodontal disease, however the use of triclosan/copolymer dentifrice reduced the frequency of deep periodontal

pockets and number of sites with additional attachment loss. The proportion of deep sites (PPD ≥6mm) at baseline was 12% in the triclosan group, remained unchanged at the final examination, while the corresponding number for the proportion of deep sites in the control group was 11% and 13% respectively. Furthermore, the percentage of deep sites with an additional attachment loss of ≥2 mm at 3 years was 1% in the triclosan group and 4% in the control group.

A further analysis of the sites with progressive attachment loss (≥2 mm) in the subjects included in the study by Rosling et al. (1997b) was performed by Furuichi and co-workers (1999). These so-called "looser sites" were exited from the longitudinal follow-up but were treated with SRP. Reduction in PPD and gain in attachment level was demonstrated for both the triclosan and control group. No significant differences were found between the two groups at baseline, at the time for SRP or at the 3-year follow-up examinations regarding mean values of BoP, PPD, PAL. However, when the change over time in PPD and PAL was evaluated for the groups there was a significantly superior reduction in PPD and gain in attachment level for the subjects brushing with triclosan/copolymer dentifrice compared with the subjects using the placebo dentifrice.

The positive effects of the use of triclosan/copolymer dentifrice reported in the studies referred to are supported by results from meta-analyses in two recent systematic reviews (Davies et al. 2004, Hioe & van der Weijden 2005). It was concluded that a dentifrice containing triclosan provides a more effective level of plaque control (weighted mean difference of -0.48 Quigley & Hein PI) and an improved gingival health (weighted mean difference of -0.26 Löe & Silness GI) compared with a regular fluoride dentifrice.

*Table 2.* Overview of selected publications on triclosan/copolymer dentifrices

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **Garcia-Godoy et al. 1990** | CCT, parallel<br>7 months<br>PI, GI<br>CE at BL, 2.5, 5, 7 months<br>Full mouth score, 6 sites/tooth | Adults, mean age 28 years<br>120 subjects, 60 test /60 control (12 dropouts)<br>PI ≥1.5<br>GI ≥1.0<br>Supragingival plaque and gingivitis on buccal & lingual surfaces of all teeth | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Supra- subgingival scaling at BL<br>OH 2x a day 1 min<br>No OHI, No IDC | Significant difference between the two groups for PI at all time points in favor of Triclosan DF ($p$ <0.05) and for GI at 5 & 7 months in favor of Triclosan DF ($p$ <0.001) |
| **Cubells et al. 1991** | CCT, parallel, double-blind,<br>6 months<br>PI, GI<br>CE at BL, 1.5, 6 months<br>Full mouth score, 6 sites/tooth-natural teeth | Adults, 18-57 years<br>120 subjects, 60 test /60 control (12 dropouts)<br>PI ≥1.5<br>GI ≥1.0 | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Supra- subgingival scaling at BL<br>OH 2x a day 1 min<br>No OHI, No IDC | Significant difference between the two groups for PI and GI at 1.5 & 6 months in favor of Triclosan DF ($p$ <0.001) |
| **Deasy et al. 1991** | CCT, parallel<br>6 months<br>PI, GI<br>CE at BL, 3, 6 months<br>Full mouth score, 6 sites/tooth | Adults, 18-65 years<br>139 subjects, >64 test />60 control (18 dropouts)<br>PI ≥1.5<br>GI ≥1.0<br>No severe periodontal disease | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Supra- subgingival scaling at BL<br>OH 2x a day 1 min<br>No OHI, No IDC | Significant difference between the two groups for PI and GI at 3 & 6 months in favor of Triclosan DF ($p$ <0.001) |
| **Lindhe et al. 1993** | CCT, parallel, double-blind<br>6 months<br>PI, GI<br>CE at BL, 6 weeks, 3, 6 months<br>Full mouth score, 6 sites/tooth | Adults, 20-45 years<br>120 subjects, 60 test /60 control (4 test /6 control dropouts)<br>≥20 teeth<br>Moderate plaque gingivitis | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>OH 2x a day 1 min<br>No OHI, No IDC | PI improved for both groups over time, GI only for Triclosan DF<br>Significant difference between the two groups for PI and GI at all follow-up time points in favor of Triclosan DF ($p$ <0.05) |
| **Binney et al. 1996** | RCT, parallel single-blind<br>3 month<br>PI, GI<br>CE at BL, 6 weeks, 3 months<br>Full mouth score | Adults, mean age 33 years<br>124 subjects<br>4 groups A-D<br>31 subjects/ group (11 dropouts)<br>PI >1.5<br>GI >1 | A.Triclosan/copolymer DF<br>B. NaF DF 1<br>C. NaF DF 2<br>D. NaF & MFP<br>Supra- subgingival scaling at BL<br>OH 2x a day<br>No OHI, No IDC | PI/GI improved for all groups over time<br>NS differences between the groups for PI & GI at 6 weeks/3 months |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **Owens et al. 1997** | RCT, parallel, single-blind<br>18 weeks<br>PI, GI<br>CE at BL, 6, 12, 18 weeks<br>Full mouth score | Adults, 18-65 years<br>143 subjects<br>4 groups A-D<br>(3 dropouts)<br>PI ≥1.5<br>GI ≥1 | A.Triclosan/copolymer DF<br>B. Triclosan/TnF<br>C. NaF DF<br>D. TnF<br>Supra- subgingival scaling at BL<br>OH 2x a day<br>No OHI, No IDC | PI/GI improved for all groups over time<br>NS differences between the groups for PI & GI at all follow-up except at 12 weeks where Triclosan/copolymer DF significantly better ($p$ <0.05) |
| **Rosling et al. 1997b** | CCT, parallel, double-blind<br>3 years<br>BoP, PPD, PAL<br>CE at BL, 6, 12, 24, 36 months<br>Full mouth score, 6 sites/tooth | Adults, mean age 55 years<br>60maintenance subjects (advanced periodontitis)<br>≥16 teeth<br>Moderate gingival inflammation<br>PPD >5 mm at 8 teeth (recurrent periodontitis) | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Recall every 3 months<br>No subgingival treatment | BoP almost unchanged over time for both groups<br>Significant difference in PPD change at 24, 36 months, decreased PPD over time Triclosan DF (0.14mm), increased PPD in Regular DF group (0.19 mm) ($p$ <0.05)<br>PAL increased in both groups (0.18/0.52 mm) |
| **Furuichi et al. 1999** | See Rosling et al. 1997b | See Rosling et al. 1997b<br>Sites with additional probing attachment loss ≥2 mm (loser sites) | See Rosling et al. 1997b<br>+ SRP in loser sites | Improvement in BoP, PPD and PAL after SRP for both groups at 36 months<br>Significant differences in PPD change (0.6 mm vs 1.7 mm) and PAL change (0.7 mm vs 1.8 mm), in favor of Triclosan DF, after SRP at 36 months ($p$ <0.05) |
| **McClanahan & Bartizek 2002** | RCT, parallel, double-blind,<br>3 months<br>PI, GI<br>CE at BL, 3 months<br>Full mouth score, 6 sites/tooth-natural teeth | Adults, 18-65 years<br>160 subjects, 80 test /80 control<br>(1 test /2 control dropouts)<br>≥20 teeth<br>PI ≥1.5<br>GI ≥1.0<br>No severe periodontal disease | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Supra- subgingival scaling at BL<br>OH 2x a day 1 min<br>No OHI, No IDC | Improvement in PI, GI for both groups at 3 months<br>NS differences in PI/GI between the two groups at 3 months |
| **Cullinan et al. 2003b** | CCT, parallel, double-blind<br>5 years<br>BoP, PPD, RA<br>CE at BL, 6, 12, 24, 36, 48, 60 months<br>Full mouth score, | Adults, mean age 39 years<br>504 "normal adult population"<br>(47 test /43 control dropouts)<br>≥16 natural teeth | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Routine dental care | NS between the two groups on LOA in all subjects<br>Statistical analyses on interproximal sites/subject with PPD ≥3.5 mm or LOA ≥2 mm;<br>Triclosan DF significant |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | 6 sites/tooth | | | fewer sites PPD ≥3.5 mm at next visit than Regular DF group ($p$ <0.001) |
| **Kerdvongbundit et al. 2003** | RCT, parallel, double-blind,<br>2 years<br>PI, GI, PPD, AL CE at BL (pre-treatment), 6, 12, 18, 24 months (post-treatment)<br>Full mouth score, 6 sites/tooth | Adults, mean age ~47 years<br>60 smoking periodontitis subjects<br>30 test /30 control<br>≥20 natural teeth | Triclosan/copolymer DF (test)<br>Regular DF (control)<br>Supra- subgingival treatment after BL<br>OH 2x a day 1 min<br>Prophylaxis every 6 months | Plaque, GI, PPD, AL improved for Triclosan DF group only<br>Significant differences in GI (0.7), PPD (1.3 mm), AL (1.1 mm) between the two groups in favor of Triclosan DF at all follow-up examinations |
| **Davies et al. 2004** | Systematic review with meta-analyses<br>Randomized studies ≥6 months<br>Search to March 2003<br>Primary outcome variable-plaque and gingival inflammation | 16 articles<br>Adult subjects with plaque and gingivitis | Triclosan/copolymer DF (test)<br>Regular DF (control) | Significant heterogeneity between studies<br>Plaque and gingivitis were significantly reduced (weighted mean difference of -0.48/-0.26) with Triclosan/copolymer DF compared with Regular DF |
| **Hioe & van der Weijden 2005** | Systematic review with meta-analyses<br>RCT/CCT<br>≥6 months<br>Search to April 2005<br>Primary outcome variable-plaque, gingivitis | 18 articles<br>Adult subjects with plaque and gingivitis<br>MT<br>No periodontitis<br>Selected for analysis 6-12 months studies | Triclosan DF (test)<br>Regular DF (control) | Significant heterogeneity between studies<br>Plaque and gingivitis were significantly reduced (weighted mean difference of -0.48/-0.24) with Triclosan DF compared with Regular DF |

## Local antibiotics

To reach the goal of secondary periodontal disease prevention, i.e. to prevent or minimize the recurrence/progression of the disease, the control of the periodontal infection is crucial. As previously described, studies have demonstrated that SPT is of great importance in maintaining stable periodontal conditions in individuals susceptible to periodontitis (Axelsson & Lindhe 1981b, Ramfjord et al. 1982, Lindhe & Nyman 1984, Axelsson et al. 2004).

Sites that are the target for treatment at recall visits for SPT are particularly those showing an increased probing pocket depth (≥5 mm) and/or bleeding on probing because of demonstrated increased risk for attachment loss at such sites (Lang et al. 1986, Badersten et al. 1990, Claffey et al. 1990, Westfelt et al. 1998). In case of persisting signs of pathology despite repeated episodes of scaling and root planing (SRP), the use of adjunctive antibiotic therapy may be considered.

The biological rational for the use of an antibiotic therapy as an adjunct to SRP is, that following the mechanical disruption of the subgingival biofilm the antimicrobial therapy may favor the elimination/suppression of periodontal pathogens and alter the ecology in the pocket (Mombelli & Samaranayake 2004, Haffajee et al. 2006). A clinical rational for considering antibiotic treatment as an adjunct to SRP in remaining deepened pockets is that repeated nonsurgical instrumentation of deep sites may have limited effect (Badersten et al. 1984, Wennström et al. 2005).

Since the maintenance patient most commonly has few sites in need of re-treatment, local application within the pocket would be the preferred method for antimicrobial drug administration. The advantages of using local delivery compared to systemic administration include (i) effective concentration of the drug at the site of infection, (ii) minimal systemic load, (iii) better patient compliance, and (iv) enhanced pharmacokinetic response (Goodson 1989).

The different types of antibiotics utilized for local delivery include tetracycline, metronidazole, minocycline and doxycycline. Table 3 presents a summary of studies evaluating the effect of locally applied antibiotics.

*Tetracycline*

The most investigated tetracycline-releasing device is the non-resorbable fiber Actisite® (controlled delivery, >24h duration of drug release). Based on meta-analysis in a recent systematic review (Bonito et al. 2005) it was shown that locally applied tetracycline fibers as adjunct to SRP results in greater PPD reduction (0.47 mm) and gain in CAL (0.24 mm) compared with the results of

SRP alone. Another systematic review comparing the treatment outcome of the two approaches (Hanes & Purvis 2003) showed a weighted mean difference of 0.21 mm in PPD reduction in favor for the adjunctive tetracycline therapy, but no difference in CAL.

In periodontal maintenance patients, it was demonstrated that the use of tetracycline fiber as an adjunct to SRP significantly enhanced the effectiveness of SRP (Newman et al. 1994, Kinane & Radvar 1999, Aimetti et al. 2004). Five-year results from a subgroup of 26 patients from the study by Newman et al. (1994) failed to substantiate the positive results of the adjunctive tetracycline fiber therapy found after 6 months (Wilson et al. 1997).

Tonetti and co-workers (1998) evaluated the effectiveness of adjunctive tetracycline fiber therapy in mandibular class II furcation sites. They showed that there was a significant additional improvement in BoP and PPD with the SRP plus tetracycline fiber compared with SRP only at 3 months, while at the final 6-month examination the difference was no longer detectable.

*Metronidazole*

The Elyzol® metronidazole gel is a resorbable sustained delivery device with 25% metronidazole (<24h duration of drug release). A meta-analysis of metronidazole as an adjunct to SRP versus SRP alone showed that the adjunctive therapy increased the PPD reduction (0.32 mm) and the gain in clinical attachment level (0.12 mm) compared to that obtained by SRP only (Bonito et al. 2005). The magnitude of the difference in PPD and CAL between the two treatments in the systematic review by Hanes & Purvis (2003) was not significant (0.06 mm/0.07 mm).

The effect of subgingival application of the metronidazole gel in combination with SRP has been compared to the effect of SRP only in periodontal maintenance patients in a number of studies (Rudhart et al. 1998, Kinane & Radvar 1999, Riep et al. 1999, Stelzel & Florés-de-Jacoby 2000). Similar clinical effects of the two treatment approaches were shown at the final examinations of the studies.

*Minocycline*

There are two different delivery devices described for local subgingival application of minocycline; ointment and microspheres. The ointment (Dentomycin®) is a resorbable sustained delivery system for the release of 2% minocycline. The microspheres for delivery of minocycline (Arestin®) is a resorbable device with controlled release of the drug. Studies (Williams et al. 2001, Meinberg et al. 2002) have shown that, used as an adjunct to SRP,

Arestin® significantly reduced PPD in untreated periodontitis patients when compared to SRP alone.

Evidence from the systematic reviews by Bonito et al. (2005) and Hanes & Purvis (2003) showed that the use of locally applied minocycline as an adjunct to SRP significantly improved the reduction in PPD and gain in CAL compared with SRP alone. Furthermore, local application of minocycline gel as monotherapy has been suggested as a treatment alternative during maintenance (McColl et al. 2006).

*Doxycycline*

A local drug delivery system for subgingival application of doxycycline is a biodegradable device with controlled release of the antibiotic (Atridox®). The systematic reviews by Bonito et al. (2005) and Hanes & Purvis (2003) demonstrated that SRP plus local application of doxycycline resulted in superior improvement in PPD and CAL compared with SRP only. (However, only one/two doxycycline studies were available and included in the analysis.)

In summary, data from systematic reviews (Hanes & Purvis 2003, Bonito et al. 2005) showed a superior effect of local application of antibiotics as an adjunctive therapy to SRP compared with SRP alone in patients with chronic periodontitis. However, most studies available evaluated the effect of the adjunctive antibiotic therapy in the initial treatment phase and the knowledge regarding its potential long-term effects when utilized as an adjunctive means during SPT are limited.

*Table 3.* Overview of selected publications on local antibiotics

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **Newman et al. 1994** | RCT, split-mouth, single-blind, multicenter (7 centers)<br>6 months<br>BoP, PPD, CAL<br>CE at BL, 1, 3, 6 months | 113 periodontal maintenance patients<br>≥ 20 years<br>2 sites in separate quadrants with PPD<br>5-8 mm, BoP+<br>2 groups (test/control)<br>(8 dropouts) | I. SRP+tetracycline fiber (Actisite) 10 days (test)<br>II. SRP (control)<br>All subjects received full mouth SRP<br>Previous maintenance care | Both groups improved in BoP, PPD, CAL at 6 months in favor for test<br>Test vs control ($p$ <0.05)<br>BoP score 37%/50%<br>PPD reduction 1.8 mm /1.1 mm<br>CAL gain 1.6 mm/1.1 mm |
| **Timmerman et al. 1996** | RCT, parallel, double-blind,<br>18 months<br>PI, GI 4 sites/tooth<br>BoP, PPD, PAL 6 sites/tooth, | 20 periodontitis patients, mean age 45 years<br>≥1 site/quadrant with PPD ≥ 5mm, LOA ≥3 mm, GI ≥1, PI ≥2<br>2 groups (test/control)<br>(No dropouts) | I. 2% minocycline gel repeated at 2 weeks, 1, 3, 6, 9, 12 months (test)<br>II. Vehicle gel (control)<br>SRP at BL, 6, 12, 15 months<br>OHI at each visit | Both groups improved in all clinical parameters at 18 months<br>PI/GI lower score in test<br>PPD reduction ~2.3 mm/2.1 mm<br>CAL gain ~1.4 for both groups |
| **Wilson et al. 1997** | RCT, split-mouth, single-blind, multicenter (2 centers)<br>5 years<br>BoP, PPD, CAL<br>CE at BL, 1, 3, 6 months, 5 years | 26 maintenance patients<br>2 groups (test/control)<br>(10 dropouts)<br>(generated from Newman et al. 1994) | I. SRP+tetracycline (Actisite) (test)<br>II. SRP (control)<br>SPT | 6 months results PPD improved for both groups in favor for test ($p$ < 0.01)<br>5 years further reduction in PPD (2.0 mm/1.6 mm)<br>CAL gain (0.7 mm/1.1 mm)<br>Greater recessions in test<br>No significant difference between groups |
| **Rudhart et al. 1998** | RCT, split-mouth, single-blind<br>175 days<br>PPD, CAL<br>CE at BL, 21, 91, 175 days | 46 periodontal maintenance patients, 27-63 years<br>≥1 tooth/quadrant PPD ≥5 mm in ≥1 interproximal site<br>2 groups (test/control)<br>(1 dropout) | I. 25% metronidazole gel (Elyzol) at day 0 and 7 (test)<br>II. SRP (control)<br>OHI at BL | Mean PPD reduction 1.6 mm for sites ≥5 mm in both groups at day 175<br>0.7 mm/0.5 mm CAL gain for test/control at 175 days |
| **Tonetti et al. 1998** | RCT, parallel, single-blind, multicenter (6 centers)<br>6 months<br>PI full mouth, BoP, PPD, recession at target sites<br>CE at BL, 3, 6 | 127 periodontal maintenance patients, mean age 48 years<br>One mandibular molar with class II furcation, BoP+, <20% full mouth PI | I. SRP+tetracycline fiber (Actisite) 10 days (test)<br>II. SRP (control)<br>No SPT | BoP reduced for 70% in test and for 52% in control group at 3 months ($p$ <0.05)<br>At 6 months reduction for 52% in both groups<br>The PPD reduction was 0.4 mm greater in test than control at 3 months |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | months | 2 groups<br>(test/control)<br>(4 dropouts) | | ($p$ <0.01)<br>No significant difference between groups at 6 months |
| **Garrett et al. 1999** | Randomized CT, parallel, single-blind<br>2 multicenter studies (10 centers)<br>9 months<br>PI, BoP, PPD, CAL<br>CE at BL, 1, 2, 4, 5, 6, 8, 9 months<br>Probing 6 sites/tooth, full mouth<br>CAL in4/5 target sites | 411 periodontitis patients/study, 25-75 years<br>≥4 pockets with PPD ≥5mm in ≥ 2 quadrants, BoP+<br>2 sites ≥7 mm<br>4 groups (I - IV)<br>(I 36/II 28 dropouts) | I. 8.5% doxycyline at BL, 4 months<br>II. Vehicle at BL, 4 months<br>III. OH<br>IV. SRP at BL, 4 months<br>Untreated quadrants no treatment<br>OHI | Improvements in PPD for all groups at 9 months<br>1.1/0.8/0.5/0.9 mm for respective group<br>CAL gain for all groups at 9 months 0.8/0.1/0.3/0.7 mm for respective group<br>Most of the improvement at 1 month<br>Re-treatment small further improvements |
| **Kinane & Radvar 1999** | RCT, parallel<br>6 months<br>PI, BoP, PPD, CAL<br>CE at BL, 6 weeks 3, 6 months | 79 previously treated periodontitis patients, mean age 45 years<br>≥ 4 teeth with PPD ≥5mm, BoP+<br>4 groups (I -IV) | I. SRP+2% minocycline (Dentomycin) (repeated after 2, 4 weeks)<br>II. SRP+tetracycline (Actisite)<br>III. SRP+ 25% metronidazole gel (Elyzol) (repeated after 7 days)<br>IV. SRP (control) | Improvement in BoP, PPD, CAL for all groups at 6 months<br>PPD reduction 1.1/1.4/0.9/0.7 mm for respective group,<br>SRP+tetracycline in favor to SRP at all time points ($p$ <0.01)<br>CAL gain of 0.5-0.7 mm for all groups,<br>SRP+tetracycline in favor |
| **Riep et al. 1999** | RCT, split-mouth, single-blind<br>3 months<br>BoP, PPD, CAL<br>CE at BL, 3 months | 30 periodontal maintenance patients, mean age 47 years<br>2 sites in 2 different quadrants<br>PPD ≥6 mm, BoP+<br>2 groups<br>(test/control)<br>(1 dropout) | I. SRP+ 25% metronidazole gel (Elyzol) 5x in 10 days (test)<br>II. SRP (control)<br>OHI when needed<br>Professional tooth cleaning 1, 3 months | 41% of test and 52% of control sites BoP+ at 3 months ($p$ <0.001)<br>Mean PPD reduction 1.7 mm for both groups at 3 months ($p$ <0.001)<br>CAL gain 1.1 mm/1.3 mm test/control ($p$ <0.001)<br>No sign difference between groups for any variable |
| **van Steenberghe et al. 1999** | RCT, parallel, double-blind, multicenter (6 centers)<br>15 months<br>PI 4 sites/tooth<br>GI, PPD, PAL 6 sites/tooth<br>CE at BL, 1, 3, 6, 9, 12, 15 months | 104 periodontitis patients, mean age 46 years<br>≥1 approximal site/quadrant with PPD ≥5 mm, LOA ≥3 mm, GI ≥1, PI ≥2<br>2 groups<br>(test/control)<br>(11 dropouts) | I. 2% minocycline gel repeated at 2 weeks, 1, 3, 6, 9, 12 months (test)<br>II. Vehicle gel (control)<br>SRP at BL, 6, 12 months<br>No OHI | Both groups improved in PPD, CAL at 15 months test/control<br>PPD reduction 1.9 mm /1.2 mm ($p$ <0.001)<br>CAL gain 0.9 mm /0.5 mm ($p$ <0.001) |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| **Stelzel & Florés-de-Jacoby 2000** | RCT, split-mouth, single-blind<br>259 days<br>BoP, PPD, CAL<br>CE at BL, 0, 91, 175, 259 days | 64 new, pretreated and recall periodontitis patients<br>≥2 sites/quadrant with PPD ≥5 mm<br>2 groups (test/control)<br>(5 dropouts) | I. SRP+ 25% metronidazole gel (Elyzol) (repeated after 7 days) (test)<br>II. SRP (control) | Improvements in BoP, PPD, CAL for both groups at 259 days<br>BoP reduction 36%/ 28% test/control ($p$ <0.05)<br>PPD reduction 1.4 mm/1.2 mm for test/control ($p$ <0.05)<br>CAL gain ~1mm for both groups<br>The improved results from SRP+metronidazole superior in untreated patients |
| **Wennström et al. 2001** | RCT, parallel, single-blind, multicenter (3 centers)<br>6 months<br>PI, BoP, PPD, CAL at BL, 3, 6 months<br>Probing 6 sites/tooth, full mouth | 105 periodontitis patients, mean age 47 years<br>≥8 sites with PPD ≥5 mm, BoP+, in 2 quadrants<br>2 sites ≥7 mm, further 2 sites ≥6 mm<br>2 groups (I,II)<br>(4 dropouts) | I. BL, full mouth SRP +OHI<br>3 months, full mouth debridement+8.5% doxycyline gel (Atridox) in sites PPD ≥5 mm in test quadrants+OHI<br>II. BL, full mouth debridement+8.5% doxycycline (Atridox) in sites ≥5 mm in test quadrants+OHI<br>3 months, SRP sites PPD ≥5 mm+OHI<br>2 control quadrants/ subject, BL SRP, 3 month debridement | BoP improved for both groups in favor for group I<br>PPD reduction for both groups at 6 months (I) 1.5 mm, (II) 1.7 mm<br>Control sites 1.4 mm/1.2 mm for respective group<br>CAL gain for both groups at 6 months 0.7/0.8 mm (I/II)<br>No significant difference in PPD, CAL gain between groups at 6 months<br>Total treatment time<br>(I) 3 h, (II) 2 h |
| **Williams et al. 2001** | RCT, parallel, single-blind, multicenter (18 centers)<br>9 months<br>BoP, PPD, CAL<br>CE at BL, 1, 3, 6, 9 months<br>Probing 6 sites/tooth | 748 periodontitis patients, mean age 48 years<br>≥4 teeth with PPD 6-9 mm, BoP+<br>3 groups (I-III)<br>(52 dropouts) | I. SRP+2%minocycline (microspheres) in sites PPD ≥5 mm, repeated 3, 6 months<br>II. SRP+vehicle in sites PPD ≥5 mm, repeated 3, 6 months<br>III. SRP<br>BL all groups full mouth SRP | Similar improvement in BoP for all groups<br>SRP+2%minocycline greater reduction in PPD at 1 month-remained over time ($p$ <0.001)<br>(PPD reduction at 9 months I/II/III; 1.3 mm/1.0 mm/1.1 mm) |
| **Eickholz et al. 2002** | RCT, parallel, double-blind, split-mouth, multicenter (3 centers)<br>6 months<br>PI, GI, BoP, PPD, RAL<br>CE at BL, 3, 6 | 111 patients with untreated or recurrent periodontitis,<br>>22 years<br>≥3 single rooted teeth with PPD 5 mm, BoP+ or PPD | I. SRP+15% doxycycline gel<br>II. SRP +vehicle<br>III. SRP<br>Initial treatment SRP, OHI<br>Maintenance at 3 | Improvements for all variables at 3, 6 months<br>3 months SRP+15% doxycycline more favorable PPD than SRP, RAL gain no significant difference<br>At 6 months SRP+15% doxycycline greater PPD |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | months<br>Probing 6 sites/tooth | ≥6 mm<br>PI <35%<br>3 groups (I-III)<br>(1 dropout) | months | reduction/RAL gain ($p$ <0.05) than both group II & III<br>(PPD reduction I/II/III; 3.1 mm/2.7 mm/2.4 mm)<br>(RAL gain I/II/III; 2.0 mm/1.6 mm/1.6 mm) |
| **Meinberg et al. 2002** | CT, parallel,<br>12 months<br>BoP, PPD<br>Probing 4 sites/ tooth<br>CE at BL, 12 months<br>(CAL in controls)<br>X-rays, BL, 12 months | 48 periodontitis patients, mean age 56 years<br>≥2 premolar/molar teeth with interproximal PPD ≥5 mm, BoP+<br>2 groups (test/control) | I. SRP only at BL, + minocycline microspheres (Arestin) in sites PPD ≥5 mm, repeated 1, 3, 6 months (test)<br>II. SRP every 3 months (control)<br>OHI if needed | Similar improvement in BoP for both groups<br>SRP+2%minocycline gel greater reduction in PPD at 12 month (0.9 mm vs 0.4 mm) ($p$ <0.05)<br>Bone loss parallel to PPD reductions (less bone loss in test) no significant difference between test/control |
| **Hanes & Purvis 2003** | Systematic review, RCT, case-controlled studies, cohort studies<br>Split-mouth/parallel design<br>≥3 months<br>Search to April 2002<br>Primary outcome PPD, CAL | 32 articles with various anti-infective agents<br>Adult chronic periodontitis patients | 3 interventions;<br>I. SRP+ local anti-infective agent<br>II. Local anti-effective agent alone<br>III. SRP alone | Meta-analysis, effects on PPD; adjunctive effect of doxycycline compared to SRP alone (All-2 studies)<br>Meta-analysis, effects on CAL; adjunctive effect of doxycycline compared to SRP alone (All-2 studies)<br>Studies reporting adjunctive effects on PPD reduction and CAL gain for sustained release anti-infective agents +SRP compared to SRP alone (weighted mean difference, 1-4 studies/group);<br>Doxycycline ; PPD 0.5 mm, CAL gain 0.3 mm<br>Metronidazole ; PPD 0.06 mm, CAL gain 0.07 mm<br>Minocycline; PPD 0. 4 mm, CAL gain 0.4 mm<br>Minocycline micro; PPD 0.3 mm, CAL loss 0.4 mm<br>Tetracycline; PPD 0.2 mm, CAL loss 0.17 mm |
| **Aimetti et al. 2004** | RCT, split-mouth, single-blind,<br>12 months<br>PI, BoP, PPD, CAL<br>CE at BL, 6, 12 months<br>Probing 6 sites/tooth | 19 previously treated periodontitis patients, mean age 47 years<br>≥4 teeth in opposite quadrants with PPD 4-5mm, | I. Two teeth SRP+tetracycline fiber (Actisite) 10 days (test)<br>II. Two teeth SRP only (control)<br>OHI every month<br>Maintenance scaling | Improvement in BoP, PPD, CAL for both groups at 6, 12 months ($p$ <0.001)<br>Test group reduced BoP/PPD/CAL gain at 12 months 76%/~2 mm/1.7 mm<br>Control group reduced |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | | BoP+, no furcation sites<br>2 groups (test/control) | 3, 6, 9 months | BoP/PPD/CAL gain at 12 months 42%/~1.2 mm/0.6 mm<br>Differences between test/control ($p$ <0.01) |
| **Tomasi & Wennström 2004** | RCT, parallel, single-blind, multicenter (3 centers)<br>3 months<br>PI, BoP, PPD, CAL CE at BL, 3 months | 103 periodontitis patients, mean age 47 years<br>≥8 sites with PPD ≥5 mm, BoP+<br>2 sites ≥7 mm, further 2 sites ≥6 mm<br>4 groups (I-IV)<br>(generated from Wennström et al. 2001) | I./II. Full mouth debridement+8.5% doxycycline gel (Atridox) in sites ≥5 mm +OHI in smokers/non-smokers (test groups)<br>III./IV. Full mouth SRP +OHI in smokers/non-smokers (control groups) | BL 22 sites PPD ≥5mm/ patient<br>BoP improved for both groups in favor for the test groups<br>PPD reduction<br>test 1.4 mm/1.6 mm (smokers/non-smokers<br>control 1.1 mm/1.5 mm (smokers/non-smokers)<br>CAL gain<br>test 0.8 mm/0.9 mm (smokers/non-smokers)<br>control 0.5 mm/0.8 mm (smokers/non-smokers) |
| **Bonito et al. 2005** | Systematic review, Search to December 2002<br>Primary outcome reductions in PPD, gain in CAL | 50 articles with various anti-infective agents<br>Adult chronic periodontitis patients | 3 interventions;<br>I. SRP+ local anti-infective agent<br>II. Local anti-effective agent alone<br>III. SRP alone | Meta-analysis<br>A. Tetracycline+SRP vs SRP;<br>Overall greater PPD reduction/CAL gain (0.5 mm/0.2 mm)<br>B. Minocycline+SRP vs SRP;<br>Overall greater PPD reduction/CAL gain (0.5 mm /0.5 mm)<br>C. Metronidazole+SRP vs SRP;<br>Overall greater PPD reduction/CAL gain (0.3 mm/0.1 mm)<br>D. Doxycycline+SRP vs SRP (only 1 study);<br>Significant greater PPD reduction/CAL gain (0.4 mm/0.4 mm) |
| **Machion et al. 2006** | RCT, parallel, single-blind<br>2 years<br>PI, BoP, PPD, RAL CE at BL, 45 days, 3, 6, 12 months, 45 days after re-treatment, 15, 18, 24 months | 48 periodontitis patients, mean age 41 years<br>≥4 sites with PPD ≥5 mm, BoP+<br>Incisors, canines<br>Smokers<br>2 groups (test/control) | I. SRP+10% doxycycline gel (Atridox) (test)<br>II. SRP+saline irrigation (control)<br>Treatment at BL, 12 months in sites with PPD ≥ 5mm, BoP+ OHI+ full moth | Compared to BL improvements in PI, BoP, PPD, CAL for both groups at 2 years ($p$ <0.05)<br>No significant difference in BoP between groups except at 45 days after re-treatment (57% vs 31% reduction) in favor for test |

| Authors | Methods | Participants | Interventions | Main findings |
|---|---|---|---|---|
| | 6 sites/tooth | (18 dropouts) | debridement at all visits | ($p$ <0.05)<br>PPD improved significantly more in test group only 45 days after treatment1.6 mm vs 1.5 mm ($p$ <0.05)<br>At 2 years PPD reduction 2.3 mm vs 2.2 mm (test/control)<br>Significantly greater RAL gain in test group at 6, 18, 24 months ($p$ <0.05)<br>24 months 1.6 mm (test), 0.7 mm (control)<br>For deep sites (PPD ≥7 mm) significant difference between test/control in favor for test, PPD at 6, 18 months, RAL gain all time points after 3 months ($p$ <0.05) |
| **McColl et al. 2006** | RCT, parallel, single-blind, pilot study<br>12 months<br>PI, BoP, PPD, CAL CE at BL, 3, 6, 9, 12 months<br>6 sites/tooth, full-mouth | 40 periodontitis patients, completed active periodontal treatment ≥6 months<br>≥40 years,<br>≥4 teeth with PPD ≥5mm, BoP+<br>PI <25%<br>2 groups (test/control)<br>(2 dropouts) | I. 2% minocycline gel in sites PPD ≥ 5 mm, BoP+ (test)<br>II. debridement only in sites PPD ≥5mm, BoP+ (control)<br>Treatment at BL, 3, 6, 9 months in sites with PPD ≥5 mm, BoP+<br>OHI when needed | Full mouth BoP score of ~18% for both groups at BL was reduced to ~9%/-10% for test/control at 12 months<br>The number of target sites/subjects was reduced with 7/subject for both groups<br>Total treatment time 79/106 min (test/control) |

## Remarks

Studying changes in clinical as well as microbiological parameters over time in subjects without clinical signs of destructive periodontal disease might provide further knowledge of importance for optimizing primary preventive strategies. An important tool in the prevention of periodontal disease is the toothbrush. Studies have demonstrated that the use of a powered toothbrush with rotation oscillation action (ROA) results in improved oral hygiene and gingival health compared with the use of a manual toothbrush. Together with the use of a toothbrush most people use a dentifrice. Evidence suggests that the use of a triclosan-containing dentifrice improves the effectiveness of supragingival plaque removal and reduces gingival inflammation. The combination of these two preventive methods might be a successful concept in periodontal disease prevention and should be investigated.

Local application of antibiotics, as an adjunct to SRP, might positively contribute to prevention of disease progression. However, few studies have investigated the clinical and microbiological effect of local antibiotics as an adjunct to SRP in "non-responding" sites in periodontal maintenance patients.

# Aims

The objectives of this series of investigations were to:

- monitor prospectively clinical parameters in adult subjects *without clinical signs of destructive periodontal disease* involved in a primary preventive program and determine the changes that may occur between yearly examinations over a 3-year period *(Study I)*

- test the hypothesis that clinical improvements observed in adult subjects *without clinical signs of destructive periodontal disease* enrolled in periodontal prevention programs, are accompanied by beneficial microbiological changes to a more host-compatible subgingival microbiota *(Study II)*

- evaluate the clinical and microbiological effects of a preventive homecare program including the combined use of a powered toothbrush and a triclosan/copolymer-containing dentifrice in adult subjects *without clinical signs of destructive periodontal disease (Study III)*

- test the hypothesis of an improved clinical and microbiological effect by means of the combined use of powered toothbrush and triclosan-containing dentifrice compared with manual toothbrush plus standard dentifrice in *patients previously treated for periodontitis* and involved in regular maintenance therapy *(Study IV)*

- evaluate long-term clinical and microbiological effects of locally applied doxycycline as an adjunct to mechanical debridement during maintenance therapy in *patients previously treated for periodontitis (Study V)*

# Materials and Methods

## Ethical considerations

The Ethics Committee at Göteborg University and the Institutional Review Board at The Forsyth Institute approved the protocols for the studies included. All participants were informed about the purpose and design of the trial and gave their written consent before they entered the study.

## Subject samples

*Studies I, II & III*

A total of 160 adult subjects without signs of destructive periodontal disease were recruited during the period January-December 2001 at 2 geographic locations (Sweden and USA). The Swedish subjects (n = 80) were recruited from the patient pool (annual recall patients) at a Public Dental Service clinic in the city of Landskrona. The USA subjects (n = 80) were recruited at The Forsyth Institute, Boston, MA, among subjects responding to an advertisement. To be included in the study a subject had to (i) be ≥20 years of age, (ii) have at least 24 natural teeth, (iii) have a maximum of 2 tooth sites with PPD >4 mm and (iv) have no proximal sites with clinical attachment loss. Subjects having systemic conditions or using drugs that could be expected to influence the onset or progression of periodontal disease, or requiring antibiotic prophylaxis for routine dental procedures, were excluded. The demographic characteristics and baseline clinical characteristics of the subject sample are presented in Table 4 and Table 5 respectively.

*Table 4.*
*Studies I, II &III.* Baseline demographic characteristics (n = 160)

| | |
|---|---|
| Mean age (range) | 38 (22 – 73) |
| Current smokers (n) | 27 |
| Females (n) | 102 |
| Ethnicity/Race (n) | |
| Caucasian | 130 |
| Other | 30 |

*Table 5.*
*Studies I & III.* Baseline clinical characteristics Mean values. 95% confidence interval

| | |
|---|---|
| Number of teeth | 27 (27.1 – 27.5) |
| Plaque (%) | 30 (27.3 – 33.5) |
| BoP (%) | 20 (17.3 – 22.4) |
| PPD (mm) | 2.3 (2.25 – 2.34) |

*Studies IV & V*

A total of 128 adult subjects previously treated for chronic periodontitis, and involved in recall programs for supportive periodontal therapy (SPT) for at least one year, were enrolled. The recruitments were performed between January 2000 and February 2002 among patients at 3 centers; two Specialist Clinics of Periodontology in the cities of Skövde (n = 30) and Göteborg (n = 30) (Sweden) and the Clinical Center for Periodontal Research, The Forsyth Institute, Boston, MA (USA) (n = 68). The inclusion criteria were: (i) ≥20 years of age, (ii) at least 15 natural teeth and (iii) a minimum of 4 teeth with a PPD of ≥5 mm. Individuals were not qualified if (i) presenting systemic conditions or using drugs that could be expected to influence the course of periodontal disease or treatment, (ii) pregnant, (iii) requiring antibiotic prophylaxis for routine dental procedures, (iv) allergic to chlorhexidine or tetracyclines or (v) having received periodontal or antibiotic therapy in the previous 3 months. The demographic characteristics and baseline clinical characteristics of the subject sample are presented in Table 6 and Table 7 respectively.

*Table 6.*
*Studies IV & V*. Baseline demographic characteristics (n = 128)

| | |
|---|---|
| Mean age (range) | 59 (34 – 82) |
| Current smokers (n) | 38 |
| Females (n) | 76 |
| Ethnicity/Race (n) | |
| Caucasian | 118 |
| Other | 10 |

*Table 7.*
*Studies IV & V*. Baseline clinical characteristics Mean values. 95% confidence interval

| | |
|---|---|
| Number of teeth | 24 (23.6 – 24.7) |
| Plaque (%) | 46 (40.5 – 51.3) |
| BoP (%) | 34 (30.4 – 37.3) |
| PPD (mm) | 3.3 (3.22 – 3.37) |
| RAL (mm) | 3.7 (3.53 – 3.90) |

## Study design

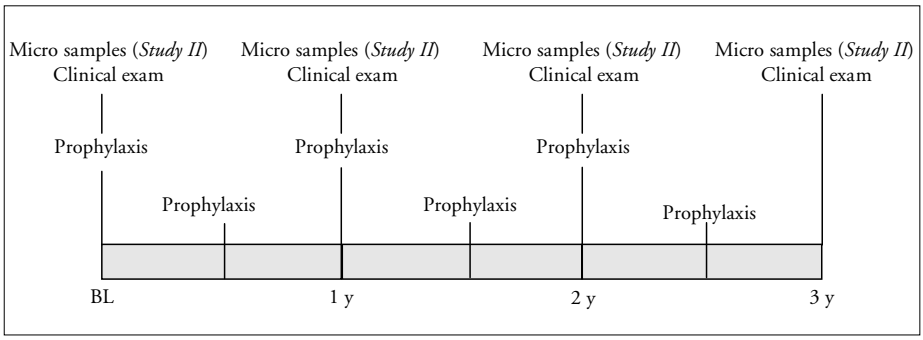
*Study I* - A prospective 3-year clinical trial (Fig. 4).

Clinical examinations were performed prior to professional prophylaxis at baseline, 1, 2 and 3 years. The participants received prophylaxis, including supragingival scaling, polishing and reinforcement of oral hygiene procedures every 6 months during the 3-year study period. The subjects were instructed to brush their teeth two times per day as well as to clean interdentally with dental floss and/or toothpicks once daily.

*Study II* - A prospective 3-year clinical trial (Fig. 4).

Subgingival plaque samplings and clinical registrations (from the sampled sites) were performed at baseline, 1, 2 and 3 years. The professional prophylaxis as well as the home-care procedures was performed as described in the design of *Study I*.

*Fig. 4.* Schematic illustration of the study design *(Study I & II)*




*Study III* - A prospective 3-year randomized controlled trial (RCT) (Fig. 5).

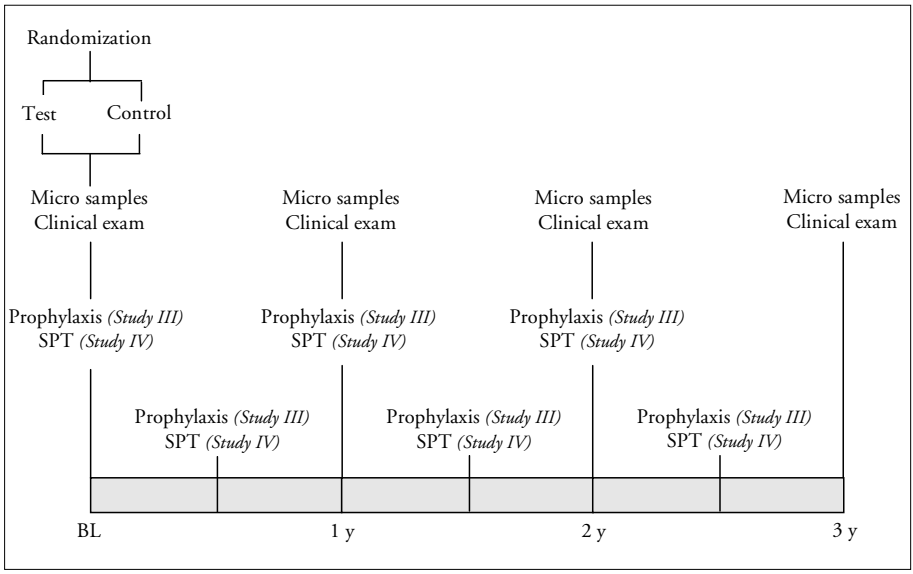
The participants in *Study III* were following a screening examination randomly assigned to one of two prevention programs, test or control. The subjects in the test group were instructed to use a powered toothbrush (Oral-B®, Gillette, Boston, MA, USA) in combination with a triclosan/copolymer/fluoride containing dentifrice (Total®, Colgate; Piscataway, NJ, USA) for their home-care procedures. The subjects in the control group received instructions in the use of a conventional manual toothbrush plus a standard fluoride-containing dentifrice (Protection Caries®, Colgate; Piscataway, NJ, USA). For both groups, the home-care procedures also included daily interdental cleaning with dental floss and/or toothpicks. At baseline and every 6 months during the 3-year study period professional performed prophylaxis, as described above *(Study I)*, was provided for both the test and the control group.

*Study IV* - A prospective 3-year RCT (Fig. 5).

Following a screening examination, the maintenance patients enrolled in *Study IV* were randomized into test and control groups. The test and control subjects were instructed in home-care programs identical to those in *Study III*. The patients continued with their interdental cleaning as instructed at previous recall visits. During the 3-year study period the participants received supportive periodontal treatment (SPT) every 6 months. The SPT included mechanical

debridement of pockets with PPD ≥5 mm, tooth polishing and reinforcement in oral hygiene procedures if needed.

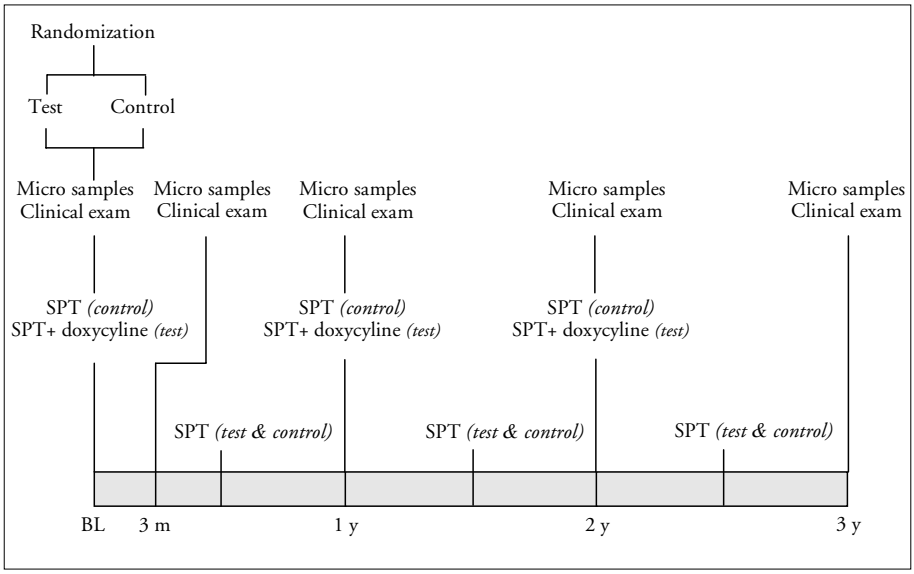
*Fig. 5.* Schematic illustration of the study design *(Study III & IV)*




*Study V* - A prospective 3-year RCT (Fig. 6).

Subsequent to the screening procedure, the patients were randomly allocated to either test or control group. At baseline, as well as at the recalls every 6 months, all subjects received mechanical debridement of sites that bled on probing and showed PPD ≥5mm. As an adjunct to the debridement locally delivered 8.8% doxycycline gel (Atridox®, Block Drug Corporation, Inc., Jersey City, NJ, USA) was applied in the test subjects at baseline, 1 and 2 years. The control subjects received mechanical debridement only. At the 6 months recalls all subjects received SPT that, in addition to the debridement, included tooth polishing and reinforcement of oral hygiene procedures. Toothbrushing was to be carried out two times per day and interdental cleaning once daily in both groups. However, during the first month after the application of the doxycycline-gel the subjects in the test group were instructed to refrain from mechanical interdental tooth cleaning and use a chlorhexidine mouth rinse solution twice daily.

*Fig. 6.* Schematic illustration of the study design *(Study V)*




## Clinical examination

Clinical examinations were performed in all studies *(I – V)*. Number of remaining teeth (third molars excluded) was recorded. The distal surface of the second molars was not included in *Studies I-III*. The examiners were calibrated with regard to the registration of the clinical parameters. The clinical measurements were recorded on data sheets and scanned into a computer. The previously recorded data were concealed from the examiner at all visits throughout the study.

*Studies I, II & III*

Clinical examinations were performed at baseline, 1, 2 and 3 years. The following clinical parameters were recorded at 6 sites (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual) at each tooth;

- Plaque; scored as present or absent (0/1) by the use of a periodontal probe along the gingival aspect of the tooth surface.
- BoP; scored as present or absent (0/1) after pocket probing within the time used for buccal or lingual probing in a jaw quadrant.
- PPD; measured as the distance from the gingival margin to the "bottom" of the gingival pocket by the use of a manual probe.

The PPD value was assessed to the nearest mm and registered twice at each visit.

In *Study II* only clinical data recorded at the mesiobuccal site of each tooth (microbiologically sampled sites) were analyzed.

*Studies IV & V*

Clinical examinations were performed at baseline, 3 months 1, 2 and 3 years. The clinical parameters described below were recorded at 4 proximal sites per tooth (mesiobuccal, distobuccal, mesiolingual and distolingual);

- Plaque; BoP and PPD; see description for *Studies I & III*
- Gingival margin (GM); assessed as the distance between the soft tissue margin and a reference point (the cemento-enamel junction or the border of a restoration) by the use of a manual probe. When the gingival margin was located apical to the reference point a negative value was set.
- Relative attachment level (RAL); calculated as PPD minus GM.

## Microbiological examination

*Studies II, III, IV & V*

Subgingival plaque samples were collected at baseline, 3 months (*Study V)*, 1, 2 and 3 years. After removal of supragingival plaque the samples were taken by the use of individual sterile curettes from the mesiobuccal aspect of each tooth (excluding third molars) and placed into separate Eppendorf tubes containing 0.15 ml Tris EDTA buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.6). 0.10 ml of 0.5 M NaOH was added immediately to each sample. All samples were processed at The Forsyth Institute. Each sample was individually evaluated for its content of 40 bacterial species using checkerboard DNA-DNA hybridization as previously described (Socransky et al. 1994, 2004). In brief, the samples were lysed and the DNA placed in lanes on a nylon membrane using a Minislot device (Immunetics, Cambridge, MA, USA). After fixation of the DNA to the membrane, the membrane was placed in a Miniblotter 45 (Immunetics), with the lanes of DNA at 90° to the lanes of the device. Digoxigenin-labeled whole genomic DNA probes to 40 bacterial species were hybridized in individual lanes of the Miniblotter. After hybridization, the membranes were washed at high stringency and the DNA probes detected using antibody to digoxigenin, conjugated with alkaline phosphatase and chemifluorescence detection. Signals were detected using AttoPhos substrate (Amersham Life Sciences, Arlington Heights, Illinois, USA). Two lanes in each run contained standards at the concentration of $10^5$ and $10^6$ cells of each species. The sensitivity of the assay

was adjusted to permit the detection of $10^4$ cells of a given species by adjusting the concentration of each DNA probe. Signals were evaluated using the Storm FluorImager (Molecular Dynamics, Sunnyvale, CA, USA, a computer-linked instrument that reads the intensity of the fluorescence signals resulting from the probe-target hybridization) and converted to absolute counts by comparison with standards on the same membrane. Failure to detect a signal was recorded as zero.

## Data analysis

The Statistical Package for the Social Sciences (SPSS, version 11.0.3., ©SPSS inc., Chicago, IL, USA) was used for performing the statistical analysis of the clinical variables and the Sun SPARC (Sun Microsystem Inc., Mountain View, CA, USA) for the statistical analysis of the microbiological data.

The sample size in the respective study was estimated to identify a mean difference in PPD of 0.3 mm with a standard deviation of 0.5 mm and a reduction of 35% to 50% in the mean percentage of sites colonized by one or more of the "red complex" species with an alpha error of 0.05 and with the power of 80%.

For description of the data mean values and 95% confidence intervals (CI) were calculated.

To evaluate statistical significant differences over time regarding clinical variables, repeated measures of ANOVA with Scheffe test for post-hoc analysis was used. Difference in microbiological parameters were analysed by the Friedman test.

For investigations of differences between groups with regard to clinical variables the unpaired *t*-test and the Chi-square test was applied and for the microbiological parameters the Mann–Whitney test.

To examine relationships between BoP and PPD values and changes over time the Spearman rank correlation coefficient was used.

To evaluate any potential relationships between the change in BoP and in PPD between baseline and 3 years and various explanatory variables (age, plaque change, prevention program, gender, country, current smoker) multiple regression models were constructed.

All microbiological analyses were adjusted for multiple comparisons.

In *Study I* the data analyses were based on the subjects who participated at all 4 examinations. BoP and PPD were considered as primary outcome variables

In *Study II* the data analyses of the microbial as well as the clinical data were based on data available from all time points from the sampled sites. The subject was regarded as the statistical unit.

In *Study III & IV* all data analyses were performed on an "intention-to-treat" basis and with the subject as the statistical unit. All subjects who entered the study were included in the analyses at all time intervals. For subjects lost during the study period the last available recordings were carried forward to represent all subsequent time points. BoP, PPD and RAL were considered as primary outcome variables.

In *Study V* the data analyses were based only on the sites that had a PPD of ≥5 mm at baseline. The analyses were performed on an "intention-to treat" basis. The primary outcome variables were those defined in *Study IV.*

# Results

*Study I*

• Number of teeth
At the start of the trial the mean number of teeth was 27. Four teeth in total were lost over the 3-year study period.

• Plaque
The mean plaque score at baseline was 28%. The plaque score level was almost unchanged during the study period.

• Bleeding on probing
A statistically significant reduction in mean BoP, from 21 % to 15 %, was observed at year 1. The improvement in BoP remained at the subsequent time intervals (Fig. 7).

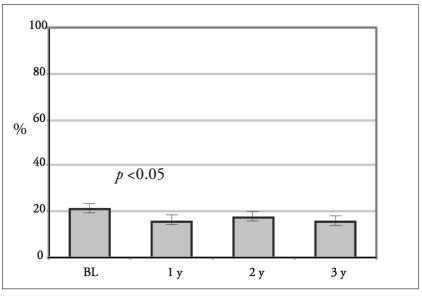



*Fig. 7.* Mean BoP score (%) at baseline, 1, 2 and 3 years ($n$ = 126). Whiskers indicate 95% confidence interval.

Almost 2/3 of the subjects showed a decrease in mean BoP score at the 1-year follow-up and there was a significant correlation between the baseline BoP value and the BoP change. For subjects with a reduction in BoP the mean BoP at baseline was 28% while subjects with an increased level had a mean value of 10%. More than 50% of all sites included did not bleed on probing at any of the examinations.

• Probing pocket depth
At baseline the mean PPD for the 126 subjects was 2.3 mm. The mean PPD was reduced with about 0.1 mm per year over the 3-year study period (Fig 8).

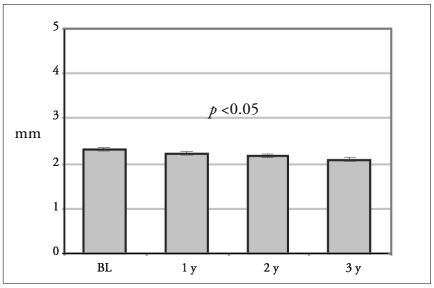



*Fig. 8.* Mean PPD (mm) at baseline, 1, 2 and 3 years ($n$ = 126). Whiskers indicate 95% confidence interval.

There was a statistically significant correlation between the baseline PPD value and the change in PPD at year 1. For the 81 participants with a reduction in PPD the mean baseline PPD was 2.4 mm while the corresponding value was 2.2 mm for those showing an increase at year 1. Nine out of the 42 subjects that demonstrated a worsening in PPD at year 1 continued to show a worsening at year 2. Further, 5 of these 9 subjects also had an additional increase in mean PPD at the final examination.

*Study II*

Microbiological data for all four visits were available in 124 subjects (in total >13.000 samples). The results demonstrated that the improvement found in clinical parameters over the study period was accompanied by a beneficial shift in the subgingival microbiota with a statistically significant decrease in the mean total DNA probe count and in mean counts of most of the 40 species investigated. The reduction was evident regardless of baseline PPD >3 or ≤3mm and was most pronounced at year 2. At the final examination most species showed some re-growth although the levels were lower compared to baseline values for the majority of species (Fig. 9).

*Study III*

Twelve subjects from the test and 22 from the control group were lost during the 3-year study period.

• Number of teeth

The mean number of teeth at baseline was 27 for both the test and the control group. Four teeth in total were lost in the test and 2 teeth in the control group during the 3 years.

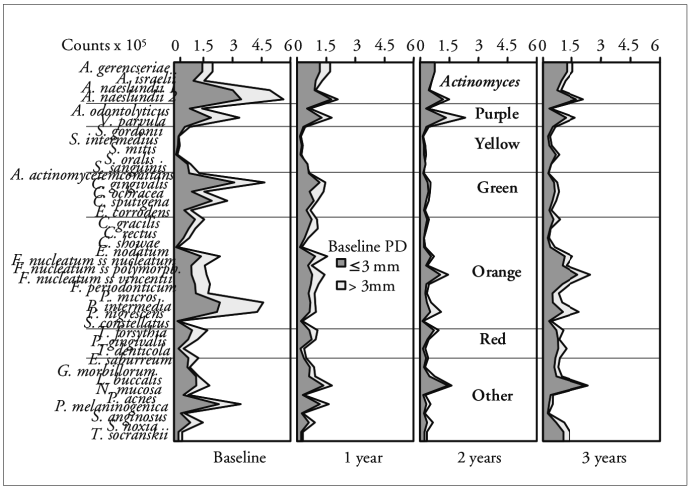



*Fig. 9.* Mean counts ($x10^5$) of 40 species from sites with baseline PPD ≤3 and >3 mm at baseline, 1, 2 and 3 years.

• Plaque

The mean plaque score at baseline was about 30% for the test and control groups and the plaque score level was more or less unaltered over time in both groups.

• Bleeding on probing

At baseline both groups showed a mean BoP score of 20%. A 25% reduction in BoP was apparent for both groups at year 1 and only minor alterations were found at subsequent time points. No statistically significant difference in mean BoP was observed between the two groups at any of the examination intervals (Fig. 10).

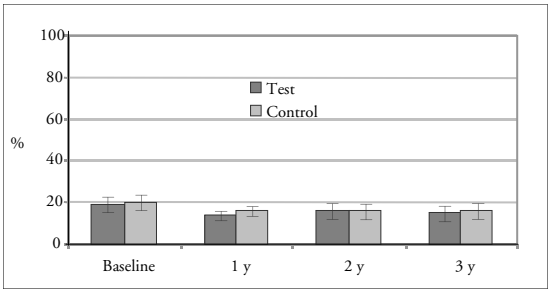



*Fig. 10.* Mean BoP score (%) for test ($n$ =80) and control groups ($n$ = 80) at baseline, 1, 2 and 3 years. Whiskers indicate 95% confidence interval.

Regarding individual change in BoP between baseline and 3 years, a decrease or no alteration in mean BoP was demonstrated for the majority of the subjects in both groups. No significant difference between test and control in this respect was observed.

The attempt to identify potential predictors for BoP change between baseline and 3 years failed.

• Probing pocket depth

A statistical significant reduction in mean PPD of 0.2 mm (2.3 mm to 2.1 mm) between baseline and 3 years was shown in both prevention groups. No statistically significant difference between the groups was found at any of the examination time points (Fig. 11).

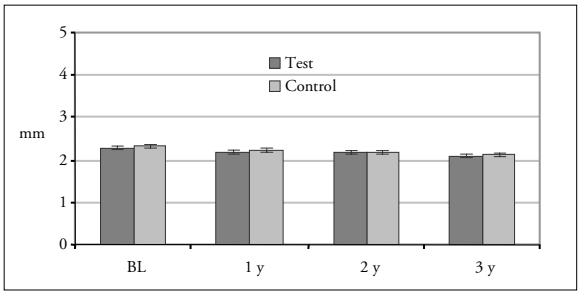



*Fig. 11.* Mean PPD (mm) for test ($n$ =80) and control groups ($n$ = 80) at baseline, 1, 2 and 3 years. Whiskers indicate 95% confidence interval.

The majority of the subjects in the test and control groups, showed an improved mean PPD value between baseline and 3 years.

None of the analyzed variables (age, gender, country, plaque/BoP change, prevention program or current smoker) was demonstrated to be a significant predictor for the PPD change over time.

• Microbiological assessments

In total >15.000 subgingival samples were analyzed. Compared to baseline the mean total DNA-probe counts were lower at all time points for both the test and the control group. The reduction in total counts, which was of similar magnitude for both groups, was most prominent at year 2 and at the final examination most species exhibited some re-growth. There were no statistically significant differences between the test and control groups in the mean counts of any of the 40 bacterial species at any time point (Fig. 12). However, for sites with initial PPD ≥4 mm there was a trend towards lower mean counts for most species in the test compared to the control group at year 2 and 3.

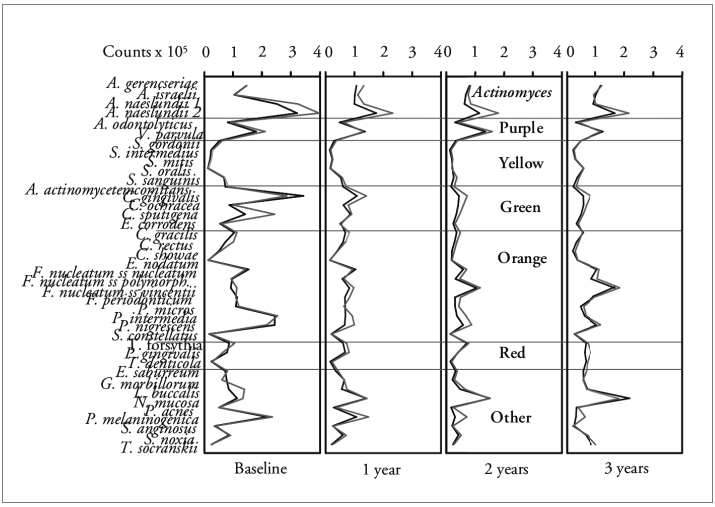



*Fig. 12.* Mean counts (x $10^5$) of 40 species for the subjects in test (—) and control (—) groups at the different examination intervals.

*Study IV*

One subject from the test and three from the control group were lost during the 3-year study period.

• Number of teeth

The participants in the test and the control group had on average 25 and 24 teeth respectively at baseline. The mean loss of teeth over the 3 years was 0.4 teeth for both groups. At the final examination about 75% of the subjects had not experienced any tooth loss.

• Plaque

At the start of the trial the test and the control group had a mean plaque score of 42% and 50% respectively. The plaque score level remained nearly unchanged over time with no statistically significant difference between the test and control groups at any time point.

• Bleeding on probing

Both groups had a mean BoP value of 34% at baseline. At the final 3-year examination a statistically significant decrease with 12% in the test and 10% in the control group was found. The difference in BoP between the test and the control group at the follow-up examination was statistically non-significant.

• Probing pocket depth

The mean PPD value at baseline was 3.3 mm for both groups. The distribution of sites within the PPD categories <4 mm, 4-5.5 mm and ≥6 mm at baseline was 70% / 25% / 4% for the test and 72% / 24% / 3% for the control group.

Compared to baseline the mean PPD for both test and control subjects were significantly reduced with 0.3 mm at the 3-year examination. Furthermore, the proportion of sites with PPD ≥4 mm was reduced from 29% (test) and 27% (control) to 25% in both groups. A majority of the patients in the two groups (>85%) demonstrated an improvement in PPD over time. About 7% of the sites with an initial PPD ≥4 mm showed at the final examination an increase in PPD of more than 1 mm and for sites with baseline PPD ≥6 mm the corresponding proportion was about 10%.

There were no statistically significant differences in PPD values between the test and the control group at any of the examination intervals.

• Relative attachment level

The mean RAL remained unchanged during the 3 years in both groups. About 50% of sites with baseline PPD ≥4 mm in both groups showed a reduction in RAL of ≥1 mm while about 12% showed a corresponding increase.

No statistically significant difference was observed between the two groups at any of the time points.

• Microbiological assessments

More than 12.000 subgingival samples were evaluated for their content of 40 bacterial species. The mean total DNA probe counts (x $10^5$ ± SEM) of 27/40 (test) and 20/40 (control) species demonstrated significant reductions over time. No statistically significant differences between the test and the control group were found at any of the evaluation intervals.

*Study V*

Three subjects from the test and one from the control group were lost during the 3-year study period. Furthermore, 25 of the experimental sites (PPD ≥5 mm at baseline) in the test group and 45 experimental sites in the control group were lost due to tooth extractions.

• Number of sites with PPD ≥5 mm

The patients in the test group had on average 11 sites with PPD ≥5 mm at baseline while in the control group the average was 14 sites. At the 3-year examination the mean number of experimental sites per subject was reduced with 6 sites in the test and with 8 sites in the control group.

• Plaque

At baseline the test and control group had a mean plaque score at experimental sites of 52% and 55% respectively, which in both groups only slightly decreased during the 3 years.

• Bleeding on probing
The mean BoP score, which at the start of the trial was 51% for the test and 56% for the control subjects, decreased significantly during the study period for both groups. In the test group the mean BoP score decreased to 37% at 3 months and further to 32% at the final examination. The corresponding figures in the control group were 50% and 38%, respectively. There was a statistically significant difference between the test and control groups in BoP score only at the 3-month examination interval.

• Probing pocket depth
The mean PPD at baseline was 5.4 mm for the test and 5.6 mm for the control subjects. At 3 years the mean PPD was significantly reduced by 1.2 mm in the test and by 1.1 mm in the control group. For both groups, the major parts of this reduction was evident already at the 3-month evaluation, and with significantly lower PPD in the test group compared to the control group. Subsequent evaluations showed no statistically significant difference between the two groups.

• Relative attachment level
There was a statistically significant RAL gain of 0.9 mm in the test and 0.7 mm in the control group between baseline and 3 years. Most of the RAL gain was demonstrated already at 3 months, 0.8 mm and 0.5 mm for the respective group. Statistically significant difference between the groups in RAL gain was found only at the 3-month evaluation.

• Microbiological assessments
Almost 1.800 subgingival samples were analyzed for their content of 40 species. In the sampled experimental sites (~3 sites/subject) the mean counts (x $10^5$, ± SEM) of 13/40 and 8/40 test species were significantly reduced over time in the test and the control group, respectively. In particular species in the green and orange complexes were significantly reduced over time in the test subjects, while in the control subjects species in the green complex showed significant reduction.

# Main findings

• In adult subjects *without clinical signs of destructive periodontal disease* that received prophylaxis every 6-month the BoP value and PPD was significantly improved over the 3 years of study (*Study I*).

• The clinical improvements obtained were accompanied by a shift to a more host-compatible subgingival microbiota (*Study II*).

• In adult subjects *without signs of destructive periodontal disease*, the long-term clinical and microbiological effects of the combined use of a powered toothbrush and a triclosan containing dentifrice were not superior to those obtained with the use of a manual toothbrush and a standard fluoride dentifrice (*Study III*).

• In *patients previously treated for periodontitis* and on regular maintenance therapy, no improved clinical or microbiological effects were demonstrated with the use of a powered toothbrush in combination with a triclosan dentifrice compared to the effects obtained by the use of a manual toothbrush and a regular fluoride dentifrice during 3 years (*Study IV*).

• In *patients previously treated for periodontitis*, local application of doxycycline as an adjunct to subgingival mechanical debridement during maintenance therapy resulted in superior clinical effects after 3 months compared to debridement alone. However, the annually repeated adjunctive antibiotic therapy had no long-term clinical or microbiological effects beyond those gained with subgingival mechanical debridement only (*Study V*).

# Discussion

The main objective of this series of prospective longitudinal clinical studies was to describe and analyze the effect of some measures for the prevention of periodontal diseases in adults. In order to investigate the prevention of occurrence/recurrence and/or further progression of periodontal diseases different categories of subjects were selected for the studies. The two categories selected were i) subjects with no clinical signs of destructive periodontal disease and ii) patients previously treated for periodontitis. All subjects included in the studies received regular supportive periodontal care and were followed over 3 years with regard to clinical and microbiological changes.

To study "real-life" effects of different prevention strategies the duration of the study is an important issue. Axelsson et al. (2004) investigated the effect of periodontal prevention over a period of 30 years, which might be regarded as a unique period of time for such a study. However, a majority of the studies that have investigated the effect of different toothbrushes, dentifrices and use of local antibiotics has a follow-up of less than 1 year (Hanes & Purvis 2003, Davies et al. 2004, Deery et al. 2004, Bonito et al. 2005, Hioe & van der Weijden 2005, Robinson et al 2006). In order to disclose "real-life" long-term effects of different prevention methods, a 3-year time frame was considered as appropriate for the current series of studies.

The design of a study is depending on the research questions to be addressed. Since the objective of *Study I* and *Study II* was to prospectively monitor clinical and microbiological parameters and to determine the changes that occurred between yearly examinations over time, an observational study design was selected. The decision to use a randomized controlled trial (RCT) design in *Study III, IV* and *V* was based on the fact that the objective for these studies was to evaluate long-term effects of different prevention methods and to avoid selection bias.

There are several sources of error in the registration and interpretation of the clinical data that must be considered. To secure the reproducibility of the assessments performed by the examiners as well as in the agreement between examiners, the examiners in the current investigations were trained to levels of accuracy in calibration sessions before the start of the studies. In addition, calibration session were scheduled and performed during the study period. To further reduce the error in PPD and GM measurement double registrations for each site were recorded and the mean value used in the analyses of the data.

Each microbiological sampling and analyzing method has its advantages and limitations. In the present investigations plaque samples were collected by the use of sterile curettes. This method of sampling was selected to obtain samples that reflect the microbial composition of the biofilm in the pocket. The checkerboard DNA-DNA hybridization technique used for the analyses of the plaque samples allows the possibility of studying large numbers of bacterial species in a high quantity of samples containing complex mixtures of microorganisms. Thus, the methods chosen for plaque sampling as well as for the microbiological analyses must be regarded as justified for the aims of the microbiological examinations in the present investigations.

## Alterations over time in subjects without signs of destructive periodontal disease

Clinical studies have demonstrated that preventive programs play an important role in the prevention of periodontal diseases in children, adolescents as well as in adults (Lövdal et al. 1961, Soumi et al. 1971, Axelsson & Lindhe 1977, 1978, 1981a, Albandar et al. 1994, Hugoson et al. 2007).

The rational behind the initiation of *Study I* & *II* was that comparatively little information was available regarding changes in periodontal and microbiological parameters that may occur over time in adult subjects with minimal clinical signs of periodontal disease involved in preventive programs. The results from *Study I* showed that there was an improvement in mean BoP and mean PPD over time. Furthermore, *Study II* demonstrated that the improvements were accompanied by a decrease in mean counts of most of the investigated species of the subgingival microbiota.

Even though the finding of an improved periodontal condition are in agreement with data previously published regarding the outcome of preventive programs based on regularly repeated mechanical self and professional performed plaque removal (e.g. Axelsson & Lindhe 1978, 1981a), it is important to clarify that in the absence of a matched control group conclusions of the impact of the preventive program on the improvements could not be drawn. In fact the improvements could be related to the so-called Hawthorne effect. This effect may be identified in almost all periodontal prevention studies as a temporary improvement in outcome variables solely because the individuals know that they are involved in a study. However, the 3-year duration of the current studies might have lowered the risk of a Hawthorne effect as the only explanation for the observed improvements over time.

With regard to the rather modest reductions observed in BoP and PPD it has to be pointed out that in subjects with minimal disease the magnitude of possible improvements are limited. In the interpretation of the data the phenomenon regression toward the mean also has to be considered.

## Effect of the combined use of powered toothbrush and triclosan-containing dentifrice

For most individuals in industrialized countries toothbrushing including a dentifrice is a part of the daily hygiene routine and hence, means to improve the effectiveness of toothbrushing should be a fruitful approach in the prevention of periodontal diseases.

Based on the evidence that ROA powered toothbrush is more effective in reducing plaque and gingivitis than a manual toothbrush (e.g. Robinson et al. 2005), and that triclosan-containing dentifrice is more effective in reducing plaque and gingivitis than a regular fluoride dentifrice (e.g. Davies et al. 2004), *Study III & IV* were designed to evaluate the effect of the combined use of the two measures in subject samples with; i) minimal periodontal disease and ii) periodontal maintenance patients. The result of both studies showed that there were no superior clinical or microbiological effects of ROA powered toothbrush in combination with a triclosan dentifrice compared with the effects of manual toothbrush and a conventional fluoride dentifrice.

The absence of significant differences in microbiological effects between the two home-care programs were in large in accordance with data previously reported from clinical trials in which the microbiological effects of the use of powered toothbrush or triclosan dentifrice were examined (Murray et al. 1989, Rosling et al. 1997a, Haffajee et al. 2001a, Cullinan et al. 2003a). Nevertheless, the absence of superior clinical effects of the combined use of the powered toothbrush and triclosan-containing dentifrice was somewhat surprising. There are however several issues that have to be considered in the interpretation of the data. Firstly, regarding the results of *Study III* it has to be pointed out that these subjects harbored almost no sites with PPD ≥4 mm. This is of importance since it was suggested by Haffajee and co-workers (2001b) that powered toothbrushing is more effective than manual in improving clinical parameters in subjects with deeper periodontal pockets. Furthermore, findings from a 5-year study by Cullinan et al. (2003b) showed that only in adult subjects with existing periodontal disease (i.e. probing pocket depths ≥3.5 mm at baseline) unsupervised daily use of a triclosan/copolymer containing dentifrice had a significant effect in slowing disease progression. Therefore, the subjects in *Study*

*III* might have had too few diseased sites in order to show additional benefit from the combined use of the powered toothbrush and the triclosan/copolymer containing dentifrice. However, *Study IV* involving patients with a comparatively large proportion of diseased sites with PPD ≥5 mm also failed to identify significant differences regarding the effects of the two home-care programs.

Secondly, all subjects in the "minimally diseased" as well as in the periodontal maintenance group of individuals performed daily interdental cleaning with dental floss, toothpicks and/or interdental brushes. This is in contrast to the majority of previous studies investigating the effect of the use of powered toothbrush or triclosan dentifrice in which the subjects were not allowed to use interdental-cleaning devices at all or were not specifically instructed in interdental cleaning. In fact, in subjects not commonly practicing interproximal cleaning the main effect of powered toothbrushes was found on interproximal-vestibular and vestibular surfaces (van der Weijden et al. 1993, 1994). However, a separate analysis performed for vestibular/lingual surfaces in *Study III* revealed no statistical differences in plaque and BoP scores or in mean PPD between the two prevention programs.

Thirdly, all subjects in *Study III & IV* can be considered well maintained, i.e. showing a relatively decent compliance and receiving regular prophylaxis/SPT. Hence, the conclusions drawn from the current studies may not be valid for non-complying individuals or for individuals who do not receive regular maintenance care. Besides supragingival treatment the SPT that was performed every 6 months in *Study IV* also included subgingival mechanical debridement of sites with PPD ≥5 mm. In contrast, no subgingival treatment was provided during maintenance in the 3-year study by Rosling et al. (1997b). The authors reported that the daily use of a triclosan/copolymer containing dentifrice reduced, in comparison to the use of regular toothpaste, the frequency of deep periodontal pockets and the number of sites exhibiting additional clinical attachment and bone loss. This difference in results between the studies may point to the importance of regularly performed subgingival debridement in limiting disease progression.

## Effect of locally delivered doxycycline as an adjunct to mechanical debridement

Recent systematic reviews from studies evaluating the effects of locally applied anti-infective agents as an adjunct to SRP revealed that there is evidence for improved clinical outcome in PPD reduction and/or gain in CAL compared to SRP alone (Hanes & Purvis 2003, Bonito et al. 2005).

The results of *Study V* demonstrated significantly improved clinical conditions of subgingival mechanical debridement plus locally applied doxycycline compared to the mechanical debridement alone at 3 months, but failed to demonstrate long-term effects (≥12 months) beyond those observed by the mechanical debridement only. This indicates that the effect of local application of controlled-release doxycycline has a limited duration. Further support for this interpretation is that the annually repeated applications of the drug did not result in any improvements in clinical and microbiological variables compared with those obtained by mechanical debridement alone at the 3-year examination interval.

A question to be asked is if locally delivered antibiotics on a more frequent basis than once/year may result in a more favorable long-term outcome. The clinical effect of repeated, locally administrated microencapsulated minocycline in patients with moderate to advanced periodontitis was evaluated in a 9-month study (Williams et al. 2001). Following SRP at baseline, sites with PPD ≥5 mm received either microencapsulated minocycline, vehicle or no adjunctive therapy. No further mechanical instrumentation was performed, but the drug application was repeated after 3 and 6 months. The authors reported that the combined therapy of SRP and microencapsulated minocycline provided significantly greater probing depth reduction than SRP alone or SRP plus vehicle. The difference was evident at 1 month and was maintained throughout the study with a mean difference of 0.24 mm at 9 months. The patients who did not receive any further treatment after baseline SRP showed some rebound in PPD, while the patients subjected to repeated local administration of microencapsulated minocycline maintained the initial PPD improvement. These results indicated that antimicrobials might have to be applied as frequent as once every 3 months to maintain a long-term beneficial effect.

One factor that partly may explain the short duration of clinical effects is that non-antimicrobial properties of locally delivered tetracycline analogues, such as the potential to counteract tissue degradation enzymes (e.g. collagenase, matrix metalloproteinase), are short-lived and may be detected only within 1 month following drug application (Oringer at al. 2002). Another issue that has to be brought up in the interpretation of the result is the standard of supragingival plaque control. Studies on the effect of locally applied tetracycline fibers as a mono-therapy (Mombelli et al. 1997) or the use of various systemically administrated antibiotics as adjunct to mechanical debridement (Kornman et al. 1994) clearly demonstrated the importance of proper oral hygiene for the benefit of the use of antibiotics in the treatment of periodontal disease. Therefore, an

inadequate standard of supragingival plaque control may account for the failure to maintain a long-term beneficial effect of the drug therapy. In fact, the use of chlorhexidine rinsing during the first month following drug application may have contributed to the positive short-term effects seen in our study.

In conclusion, although short-term beneficial effects on clinical parameters were demonstrated with adjunctive use of locally delivered doxycycline in periodontal maintenance patients, repeated application once annually seems to have no long-term clinical or microbiological effects beyond those observed by subgingival mechanical debridement alone.

# Conclusions and future considerations

Adult subjects without clinical signs of destructive periodontal disease and involved in preventive programs may improve clinically and microbiologically in a long-term perspective. A home-care program including toothbrushing with a powered toothbrush plus a triclosan dentifrice in such a group of individuals, that also mechanically clean their teeth interdentally, may not offer any superior long-term effects on clinical or microbiological parameters beyond those obtained by the use of a manual toothbrush and a regular fluoride dentifrice.

Patients previously treated for periodontitis and who receive regular supportive periodontal therapy may improve their periodontal condition and microbiological status over time. The use of powered toothbrush in combination with a triclosan dentifrice may not result in clinical or microbiological parameters superior to those obtained by the use of manual toothbrush plus a regular fluoride dentifrice. Subgingival mechanical debridement plus local application of doxycycline in sites with clinical signs of pathology in this category of patients may have superior short-term effects on clinical parameters compared to mechanical debridement alone. However, the annual application of the adjunctive antibiotic therapy had no long-term clinical or microbiological effects beyond those obtained by subgingival mechanical debridement only.

Since the results indicated that the standard of oral hygiene affects the treatment outcome of antibiotic therapy, further studies are indicated to fully explore the potential benefit of local antibiotic therapy as part of SPT.

Evaluations of periodontal prevention/treatment procedures should include patient centered outcomes and not only surrogate endpoints. Since this issue is not considered in the majority of prevention/treatment studies future research has to include such variables. Furthermore, the cost-benefit aspect of periodontal prevention for the society as well as for the individual needs to be further investigated.

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