Novel findings on anti-plaque effects of stannous fluoride

TAO HE, PHD, DDS, **YUANSHU ZOU**, PHD, **JOE DIGENNARO**, MS & **AARON R. BIESBROCK**, DMD, PHD, MS

ABSTRACT: Purpose: To evaluate the antiplaque effects for 0.454% bioavailable gluconate chelated stannous fluoride (SnF_2) dentifrices versus controls by clinical model, plaque index, tooth surface and tooth type in a pooled analysis. **Methods:** Randomized controlled trials (RCTs) were conducted to evaluate plaque effects of SnF_2 dentifrices from the same formulation family over the past 30 years. Forty-four 4-day and longer-term (≥ 2 weeks) RCTs conducted in six countries with 3,336 subjects using Turesky Modified Quigley-Hein Plaque Index, Rustogi Modification of the Navy Plaque Index, Digital Plaque Imaging Analysis, and Silness and Löe Plaque Index were included. **Results:** In 13 and 11 longer-term studies assessing SnF_2 dentifrice versus a negative or positive control, respectively, standardized differences in average plaque score of -1.15 (95% CI: -1.61, -0.69) and -0.74 (95% CI: -1.20, -0.28) were observed ($P \leq 0.011$), favoring SnF_2. Reductions represented a 19% and 16% benefit versus the negative and positive control, respectively. In 18 and five 4-day studies assessing SnF_2 dentifrice versus a negative (NaF/SMFP) or positive (triclosan/chlorhexidine) control, respectively, differences in average 4-day plaque score of -0.27 (95% CI: -0.31, -0.23) and -0.15 (95% CI: -0.25, -0.06) were observed ($P \leq 0.001$) favoring SnF_2. Reductions represented a 14% and 11% benefit versus the negative and positive control, respectively. Significant antiplaque benefits for SnF_2 dentifrice were seen regardless of clinical model, plaque index, tooth surface or type, including brushed and unbrushed surfaces ($P \leq 0.049$). (*Am J Dent* 2022;35:297-307).

CLINICAL SIGNIFICANCE: Bioavailable gluconate chelated SnF_2 dentifrices showed consistent plaque inhibition versus negative and positive controls across all conditions evaluated. Importantly, the effect on unbrushed surfaces illustrated the significant plaque inhibition benefit of SnF_2 beyond mechanical plaque removal.

✉: Dr. Aaron Biesbrock, The Procter & Gamble Company, 8700 Mason-Montgomery Road, Mason, OH 45040, USA. E-✉: biesbrock.ar@pg.com

Introduction

Dental plaque is a primary etiological factor in the development of both caries and periodontal disease, conditions that represent a major global disease burden with negative impacts on quality of life as well as economic costs to society.[1-3] The caries process is complex and is driven by acid production resulting from bacterial plaque metabolism of dietary sugars. Over time, these acids permanently cavitate the tooth enamel.[1] Accumulation of plaque at and below the gingival margin can lead to gingival inflammation and bleeding that may progress to periodontitis in susceptible individuals.[2] As the inflammation process advances, periodontitis can cause irreversible destruction of tooth-supporting tissues and eventual tooth loss.[1]

Mechanical plaque removal measures alone are often insufficient for preventing caries and periodontal disease. Plaque is frequently left behind with toothbrushing, the most common method of mechanical plaque removal, due to improper brushing technique, inadequate brushing duration or frequency, or a combination of these factors.[4,5] In addition, most patients do not follow professional recommendations for cleaning interproximal tooth surfaces, the predominant sites of residual plaque.[6,7] Recent findings[8] indicate that poor oral hygiene can alter the oral microbiome in as little as 24 hours, accelerating its aging faster than previously known. Given these obstacles, chemotherapeutics that reduce the metabolic activity of remaining plaque and inhibit plaque regrowth are an important complement to mechanical plaque removal strategies.[9]

Stannous fluoride (SnF_2) has been shown to provide superior benefits compared with other fluorides in randomized controlled trials (RCTs) on a broad range of outcomes, including reduction of plaque,[10] gingivitis,[10,11] erosion,[12,13] and sensitivity.[12,13] The unique properties of SnF_2, namely its instability in aqueous mediums, pose important formulation challenges that can result in differing levels of stannous bioavailability and, consequently, clinically significant differences in antimicrobial efficacy across dentifrices.[14-17] Consistent with this, a randomized, double-blind, parallel group study found significant differences in reduction in gingival bleeding sites among 0.454% SnF_2 dentifrices with differing formulation parameters.[17] The antiplaque effects of SnF_2 dentifrices in previous meta-analyses/pooled analyses have been somewhat mixed,[18,19] a finding that may be attributed in part to differences in formulation compositions and levels of bioavailable SnF_2 across the dentifrices evaluated.

This paper reports on a pooled analysis of RCTs conducted over the past 30 years on 0.454% gluconate chelated SnF_2 dentifrices from the same formulation family with optimized stannous bioavailability, to assess their effects on plaque control across plaque indices, clinical models, and by tooth surface and type. A pooled analysis of a specific formulation family was chosen over a systematic review to ensure access both to analytical records confirming SnF_2 bioavailability and to individual subject-level data needed to fulfill the test plan.

Materials and Methods

These pooled analyses were conducted in agreement with the general principles of the PRISMA guidelines[20] and followed a methodology as reported previously.[11,12]

Search - A search limited to the Procter & Gamble Oral Care Clinical archive (SnF_2 gluconate) was undertaken to identify all relevant studies that fit the inclusion criteria (PICOs) with results available as of June 2020 for inclusion in this pooled analysis.

Table 1a. Longer-term RCTs assessing plaque effects of SnF_2 dentifrice.

Study	Year study initiated	Location	Plaque index	Inclusion criteria	Control	Timepoint included	Baseline mean	End of treatment mean (SE)	N
LT-1[30]	1988	Indiana, USA	SLPI	Only gingivitis criteria	Negative: NaF	12 weeks	0.97	SnF_2 0.77 (0.019)	
								NC 0.82 (0.028)	412
LT-2[31]*	1992	Indiana, USA	TQHPI	Only gingivitis criteria	Negative: NaF			SnF_2 1.99 (0.030)	
					Positive: Triclosan/NaF	12 weeks	1.91	NC 2.07 (0.030)	
								PC 2.09 (0.030)	545
LT-3[32]	2002	Florida, USA	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	2.81	SnF_2 2.24 (0.049)	
								NC 2.38 (0.049)	133
LT-4[33]	2003	Florida, USA	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	2.86	SnF_2 2.12 (0.039)	
								NC 2.28 (0.048)	132
LT-5[34]	2007	Florida, USA	TQHPI	Evidence of plaque and gingivitis	Negative: SMFP	11 weeks	2.98	SnF_2 1.99 (0.063)	
								NC 2.16 (0.058)	84
LT-6	2007	Florida, USA	DPIA	Evidence of plaque	Negative: SMFP	3 weeks	0.15	SnF_2 0.10 (0.009)	
								NC 0.16 (0.010)	43
LT-7	2012	Nevada, USA	RMNPI	Evidence of plaque	Negative: SMFP	12 weeks	0.66	SnF_2 0.41 (0.022)	
								NC 0.59 (0.010)	48
LT-8[35]	2012	Massachusetts, USA	DPIA	Overnight plaque accumulation	Negative: SMFP	6 weeks	0.12	SnF_2 0.06 (0.007)	
								NC 0.10 (0.011)	45
LT-9[36]	2017	Florida, USA	DPIA	Adults with plaque	Negative: SMFP	4 weeks	0.11	SnF_2 0.07 (0.010)	
								NC 0.10 (0.009)	46
LT-10[37]	2018	California, USA	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	1.69	SnF_2 1.12 (0.020)	
								NC 1.72 (0.026)	74
LT-11[38]	2018	Nevada, USA	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	3.00	SnF_2 2.16 (0.065)	
								NC 2.67 (0.042)	86
LT-12[39]*	2019	Israel	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	4.05	SnF_2 3.33 (0.043)	
					Positive: NaF with Zn/Arg			NC 3.65 (0.065)	
								PC 3.53 (0.062)	153
LT-13[40]	2019	Nevada, USA	TQHPI	Only gingivitis criteria	Negative: SMFP	12 weeks	2.95	SnF_2 2.02 (0.038)	
								NC 2.71 (0.038)	100
LT-14[41]	2011	Florida, USA	DPIA	Adults with plaque	Positive: Triclosan/NaF	3 weeks	0.14	SnF_2 0.08 (0. 007)	
								PC 0.20 (0. 028)	46
LT-15	2009	Florida, USA	DPIA	Evidence of plaque on anterior teeth	Positive: Triclosan/NaF	2 weeks	N/A	SnF_2 0.09 (0.009)	
								PC 0.09 (0.009)	49
LT-16[42]	2009	Brazil	DPIA	Evidence of plaque on anterior teeth	Positive: Triclosan/NaF	2 weeks	N/A	SnF_2 0.11 (0.016)	
								PC 0.12 (0.016)	50
LT-17	2011	Guatemala	RMNPI	RMNPI $\geq$ 0.5	Positive: Triclosan/NaF	6 weeks	0.6	SnF_2 0.16 (0.007)	
								PC 0.18 (0.007)	119
LT-18[43]	2011	Indiana, USA	DPIA	Evidence of overnight plaque	Positive: Triclosan/NaF	3 weeks	0.15	SnF_2 0.12 (0.008)	
								PC 0.14 (0.008)	93
LT-19[44]	2011	Nevada, USA	RMNPI	RMNPI $\geq$ 0.5	Positive: Triclosan/NaF	6 weeks	0.63	SnF_2 0.28 (0.010)	
								PC 0.50 (0.010)	114
LT-20	2011	Mainz, Germany	DPIA	Evidence of overnight plaque	Positive: Triclosan/NaF	3 weeks	0.14	SnF_2 0.10 (0.008)	
								PC 0.11 (0.008)	96
LT-21[45]	2016	Missouri, USA	RMNPI	RMNPI $\geq$ 0.5	Positive: Triclosan/NaF	4 weeks	0.62	SnF_2 0.41 (0.007)	
								PC 0.53 (0.007)	118
LT-22	2017	Israel	RMNPI	Measurable dental plaque	Positive: Chlorhexidine rinse	4 weeks	0.71	SnF_2 0.53 (0.009)	
								PC 0.53 (0.009)	68

*Positive and negative control.

RCT, randomized controlled trial. Plaque indices: DPIA, Digital Plaque Imaging Analysis; RMNPI, Rustogi Modification of the Navy Plaque Index; SLPI, Silness and Löe Plaque Index; TQHPI, Turesky Modified Quigley-Hein Plaque Index. Dentifrice/control ingredients: NaF, sodium fluoride; SMFP, sodium monofluorophosphate; SnF_2, stannous fluoride; Zn/Arg, zinc/arginine.

Eligibility criteria - Data were included from 4 days to 3 months from RCTs that had intervention and control groups in human subjects and reported the effects of a family of 0.454% bioavailable SnF_2 dentifrices on plaque outcomes. PICO model was employed: Patient: adult subjects; Intervention: family of 0.454% bioavailable gluconate chelated SnF_2 dentifrices from a single manufacturer (The Procter & Gamble Company); Comparator: positive (triclosan dentifrice or chlorhexidine rinse) or negative control (sodium fluoride or sodium mono-fluorophosphate dentifrice); Outcome measures: plaque inhibition efficacy as measured using the Turesky Modified Quigley-Hein Plaque Index (TQHPI),[21,22] the Rustogi Modification of the Navy Plaque Index (RMNPI),[23] Digital Plaque Imaging Analysis (DPIA),[24] and the Silness and Löe Plaque Index.[25] The studies included in these pooled analyses were selected because the chemical profiles of the bioavailable SnF_2 gluconate chelated dentifrices were well-characterized delivering bio-available SnF_2, and access to subject-level data allowed for additional analysis by tooth type. RCTs using the 4-day crossover model included lingual brushing only; buccal surfaces were only exposed to dentifrice slurry.

Clinical plaque indices - The indices used to assess plaque in these studies are well-published and validated. The Turesky Modified Quigley-Hein Plaque Index assesses disclosed plaque on two sites per tooth (facial and lingual) using a 0 to 5 scale, where 0 = no plaque/debris and 5 = plaque covering 2/3 or more of tooth crown.[21,22] The Rustogi Modification of the Navy Plaque Index (RMNPI)[23] scores disclosed plaque as absent (0) or present (1) on nine areas of the buccal and lingual surfaces of

Table 1b. 4-day plaque RCTs assessing plaque effects of SnF_2 dentifrice.

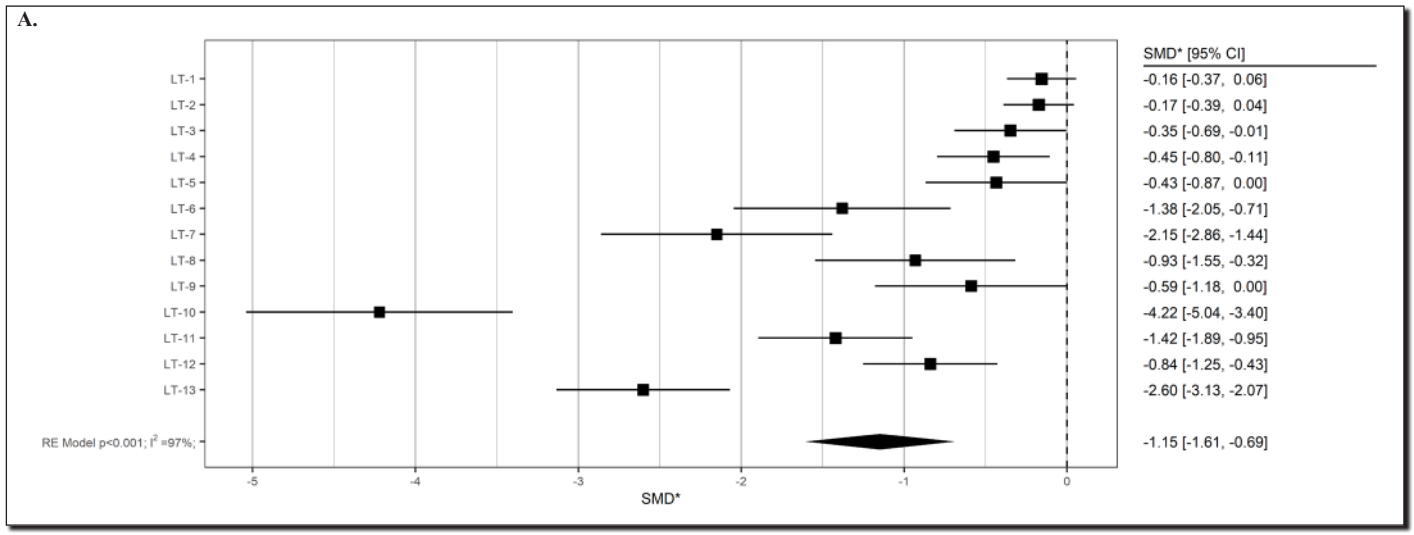
Study	Year	Location	Plaque index	Inclusion criteria	Control	Baseline mean	End of treatment mean (SE)	N
4D-1[46]	2008	Ohio, USA	TQHPI	No plaque inclusion criteria specified	Negative: SMFP	1.94	SnF_2 1.26 (0.06) NC 1.47 (0.06)	25
4D-2[46]	2008	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	1.59	SnF_2 1.28 (0.06) NC 1.53 (0.06)	27
4D-3[46]*	2008	Ohio, USA	TQHPI	Previously identified plaque formers Positive: Triclosan/NaF	Negative: SMFP	1.89	SnF_2 1.08 (0.04) NC 1.56 (0.05) PC 1.40 (0.05)	29
4D-4	2010	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.22	SnF_2 2.05 (0.05) NC 2.25 (0.06)	29
4D-5	2010	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	1.89	SnF_2 1.25 (0.07) NC 1.57 (0.07)	28
4D-6	2011	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.28	SnF_2 2.01 (0.08) NC 2.37 (0.08)	28
4D-7	2012	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.47	SnF_2 1.84 (0.07) NC 2.12 (0.08)	30
4D-8	2013	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.6	SnF_2 2.11 (0.05) NC 2.47 (0.06)	36
4D-9	2014	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.7	SnF_2 2.31 (0.05) NC 2.62 (0.06)	36
4D-10	2014	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.11	SnF_2 1.22 (0.06) NC 1.61 (0.07)	29
4D-11	2015	Xian, China	TQHPI	Previously identified plaque formers	Negative: NaF	2.36	SnF_2 2.25 (0.03) NC 2.45 (0.03)	30
4D-12	2015	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.58	SnF_2 2.20 (0.05) NC 2.31 (0.05)	33
4D-13	2017	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.2	SnF_2 1.56 (0.05) NC 1.78 (0.06)	32
4D-14	2018	Beijing, China	TQHPI	Adults with plaque	Negative: NaF	3.54	SnF_2 2.95 (0.03) NC 3.35 (0.03)	40
4D-15	2018	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.19	SnF_2 1.52 (0.06) NC 1.72 (0.07)	31
4D-16	2019	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.17	SnF_2 1.66 (0.05) NC 1.91 (0.05)	32
4D-17	2019	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.44	SnF_2 1.76 (0.04) NC 1.98 (0.04)	30
4D-18	2019	Ohio, USA	TQHPI	Previously identified plaque formers	Negative: SMFP	2.24	SnF_2 1.72 (005) NC 1.91 (0.06)	32
4D-19[47]	2011	New Jersey, USA	TQHPI	Previously identified plaque formers	Positive: Triclosan/NaF	2.56	SnF_2 1.57 (0.08) PC 1.72 (0.08)	28
4D-20	2011	Shanghai, China	TQHPI	Previously identified plaque formers	Positive: Triclosan/NaF	3.03	SnF_2 2.60 (0.03) PC 2.64 (0.03)	36
4D-21	2014	New Jersey, USA	TQHPI	Previously identified plaque formers	Positive: Triclosan/NaF	2.63	SnF_2 1.46 (0.08) PC 1.59 (0.08)	29
4D-22	2016	Ohio, USA	TQHPI	Previously identified plaque formers	Positive: Triclosan/NaF	2.05	SnF_2 1.23 (0.04) PC 1.39 (0.04)	32

*Positive and negative control.
RCT, randomized controlled trial. RCT, randomized controlled trial. Plaque indices: TQHPI, Turesky Modified Quigley-Hein Plaque Index. Dentifrice/control ingredients: NaF, sodium fluoride; SMFP, sodium monofluorophosphate; SnF_2, stannous fluoride.

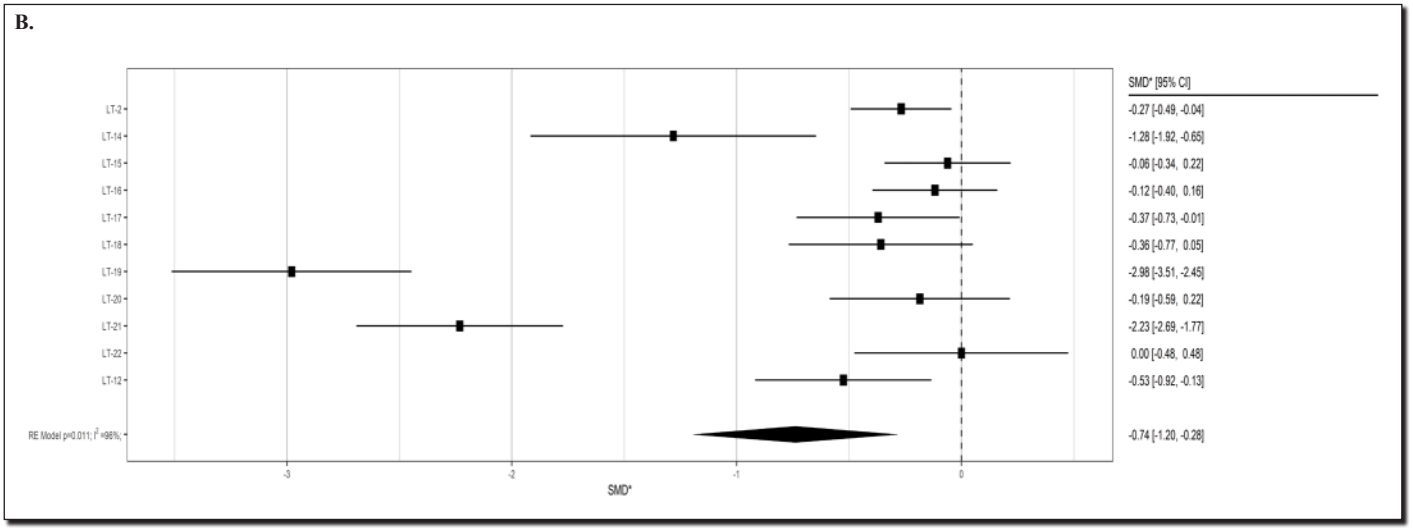
each scorable tooth, for a total of 18 sites per tooth. Silness and Löe Plaque Index[25] evaluates the presence of plaque on four surfaces of each tooth (buccal, lingual, mesial, and distal) using a 0 to 3 score, where 0= no plaque and 3 = abundance of soft matter within the gingival pocket and/or on tooth and gingival margin. Digital Plaque Imaging Analysis (DPIA)[24] objectively evaluates total dental plaque. A digital image of fluorescein-disclosed plaque, illuminated by ultraviolet (UV) light, is taken and tooth plaque is identified by a unique color value. Tooth plaque is then calculated by summing the number of pixels in that color category and then calculating the percentage of the tooth covered with dental plaque.

Study selection and data extraction - Two authors (TH and YZ) independently assessed the eligibility of all studies retrieved from the archives. Disagreements between the evaluators regarding the selected studies were resolved by discussion. The following data were extracted from the studies included in the final analysis: study name and year; country; study design; participants; age and gender; intervention; follow-up period; oral health condition; and values of outcome measurements (subject-level data, sample size, means and standard deviations) in both intervention and control groups. The assessment up to and including the 3-month visit for data was used if the study had more than one follow-up visit.

Risk of bias assessment - The quality of the included individual RCTs was assessed according to the revised Cochrane collaboration RoB tool for randomized parallel group and crossover trials.[26] RoB 2 has five domains of bias focused on different aspects of study design, conduct, and reporting. Within each of the five domains, a series of signaling questions elicits information about study features and a risk of bias judgement (low risk, some concerns, and high risk) is proposed based on an algorithm. Each study was assigned a risk of bias judgement accordingly.



* SMD=Standardized Mean Difference (Stannous-Negative Control).



* SMD=Standardized Mean Difference (Stannous-Positive Control).

Fig. 1. Longer-term (≥ 2 weeks) plaque studies versus a negative control (A) and positive control (B).

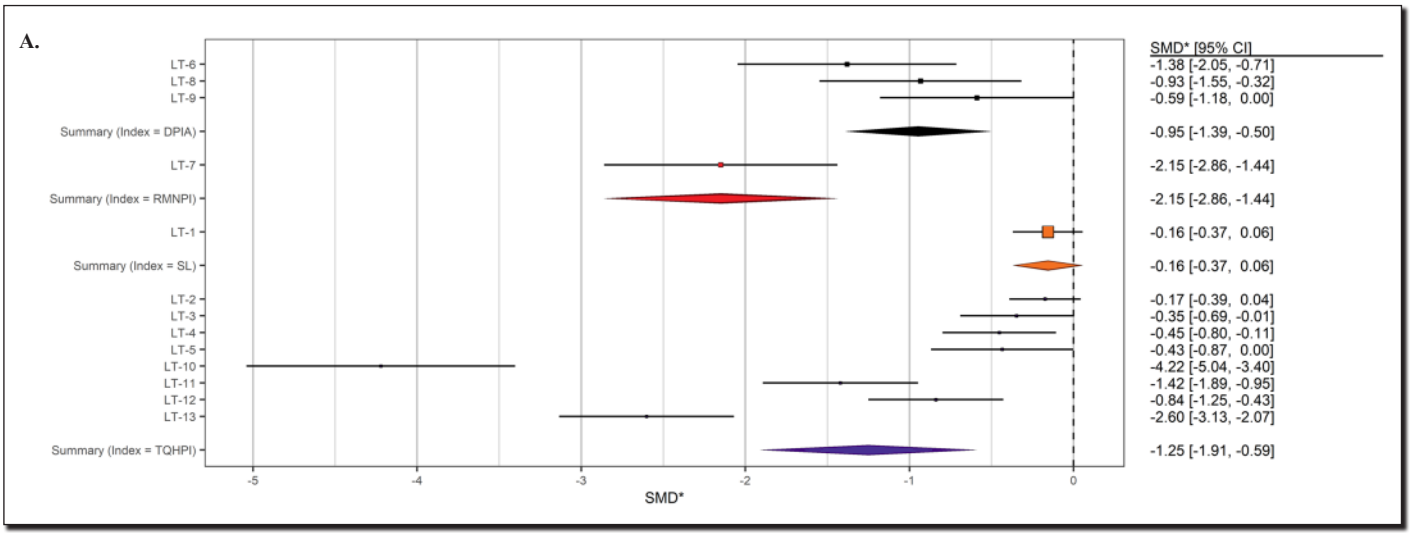
Statistical analysis - For longer term plaque studies, the efficacy variables (TQHPI: eight studies, DPIA: eight studies, Silness and Löe Plaque Index: one study and RMNPI: 5 studies) were standardized by dividing the mean treatment difference in each study by that study's standard deviation (Cohen's d), which was then used to generate comparisons across studies using pooled analysis. Results included plaque assessments from 2 to 12 weeks. For both longer-term and 4-day studies (TMQHI: 22 studies) the generic inverse variance method with random-effects model was used to calculate the summary differences between the SnF_2 dentifrice and the controls (both positive and negative controls). For studies with multiple interventions or controls, the weighted average of the scores and pooled standard deviation were calculated to obtain a single pairwise comparison and to mitigate the unit-of-analysis error. Paired analyses were conducted for all 4-day trials. Effect sizes (Cohen's d) were also calculated using standardized mean difference for 4-day studies. Effect size is one of the most important indicators of clinical significance with < 0.2 = trivial effect; 0.2-0.5 = small effect; 0.5-0.8 = moderate effect; > 0.8 = large effect.[27]

The principal summary measure was the estimated mean differences, presented in forest plots along with the 95% confidence intervals (CIs). Tests for overall effects were based on z-statistics and associated p-values. Percent change from control was calculated by the weighted percent change from the control from different studies where the weights were calculated from the random effects model.

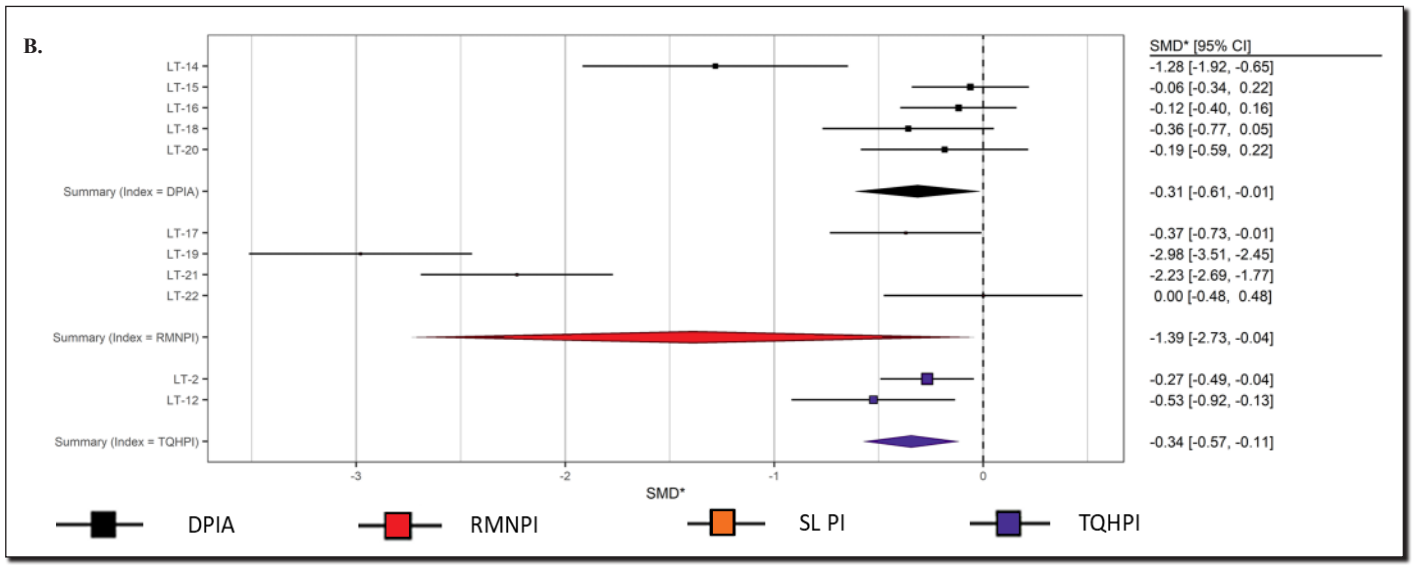
Pooled analyses were also done on different tooth surface or type using site-level data. A sub-dataset of studies was chosen for these analyses that used the same clinical index (Turesky Modified Quigley-Hein Plaque Index). The statistical heterogeneity was quantified using the I^2 statistic which is reported in the forest plots. An I^2 statistic of 30-60% represents moderate heterogeneity, an I^2 statistic of 50-90% represents substantial heterogeneity, and an I^2 statistic of 75-100% represents considerable heterogeneity. All summary-level and site-level pooled analyses were conducted using the "metafor" package in R version 3.2.3.[28,29]

Results

Forty-four RCTs were identified assessing plaque based on TQHPI, RMNPI, DPIA, and Silness and Löe Plaque Index.[30-47] The studies were conducted in six countries and involved 3,336



* SMD=Standardized Mean Difference (Stannous-Negative Control).



* SMD=Standardized Mean Difference (Stannous-Positive Control).
DPIA, Digital Plaque Imaging Analysis; RMNPI, Rustogi Modification of the Navy Plaque Index; SL PI, Silness and Löe Plaque Index; TQHPI, Turesky Modified Quigley-Hein Plaque Index.

Fig. 2. Longer-term (≥ 2 weeks) plaque studies by method versus a negative control (A) and positive control (B).

subjects. Twenty-two studies were longer-term (≥ 2 weeks) plaque studies[30-45] and 22 were 4-day plaque studies[46,47] (Table 1).

Analysis of longer-term studies - In 13 longer-term studies assessing SnF_2 dentifrice versus a negative control, a standardized difference in the average plaque score of -1.15 (95% CI: -1.61, -0.69) was observed favoring SnF_2 dentifrice, equating to a 19% benefit versus the negative control (P< 0.001) (Fig. 1A). In 11 longer-term studies assessing SnF_2 dentifrice versus a positive control, a standardized difference in the average plaque score of -0.74 (95% CI: -1.20, -0.28) was observed favoring SnF_2 dentifrice, equating to a 16% benefit versus the positive control (P= 0.011) (Fig. 1B). Effect sizes (Cohen's d) using standardized mean differences (-1.15 and -0.74) indicate large and moderate effects when comparing SnF_2 dentifrice with negative and positive controls, respectively.

Analysis of longer-term studies by plaque index - The pooled analyses of longer-term RCTs comparing SnF_2 dentifrice to controls by plaque assessment method are shown in Figs. 2A and B. Among 13 longer-term studies assessing SnF_2 dentifrice versus a negative control, standardized differences in average plaque scores of -0.95 (95% CI: -1.39, -0.50), -2.15 (95% CI: -2.86, -1.44), -0.16 (95% CI: -0.37, 0.06), and -1.25 (95% CI: -1.91, -0.59) were seen favoring SnF_2 relative to the negative control as measured by DPIA (three studies), RMNPI (one study), Silness and Löe Plaque Index (one study), and TQHPI (eight studies), respectively (Fig. 2A). Among 11 longer-term studies assessing SnF_2 dentifrice versus a positive control, standardized differences in average plaque scores of -0.31 (95% CI: -0.61, -0.01), -1.39 (95% CI: -2.73, -0.04), and -0.34 (95% CI: -0.57, -0.11) were seen favoring SnF_2 relative to the positive control as measured by DPIA (five studies), RMNPI (four studies) and TQHPI (two studies), respectively (Fig. 2B).

Analysis of 4-day studies - In eighteen 4-day studies assessing SnF_2 dentifrice versus a negative control, a difference in the average 4-day plaque score of -0.27 (95% CI: -0.31, -0.23) was

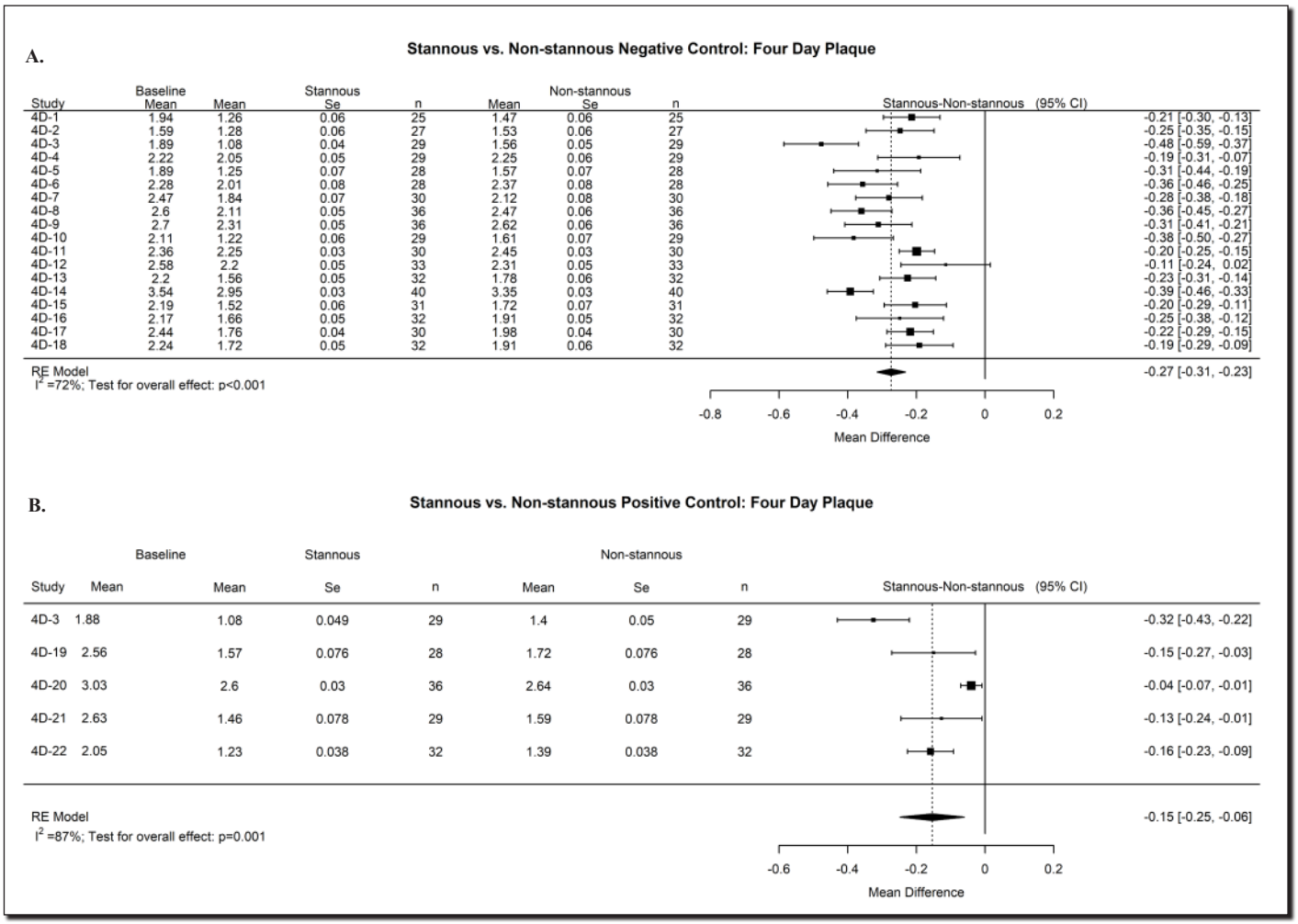


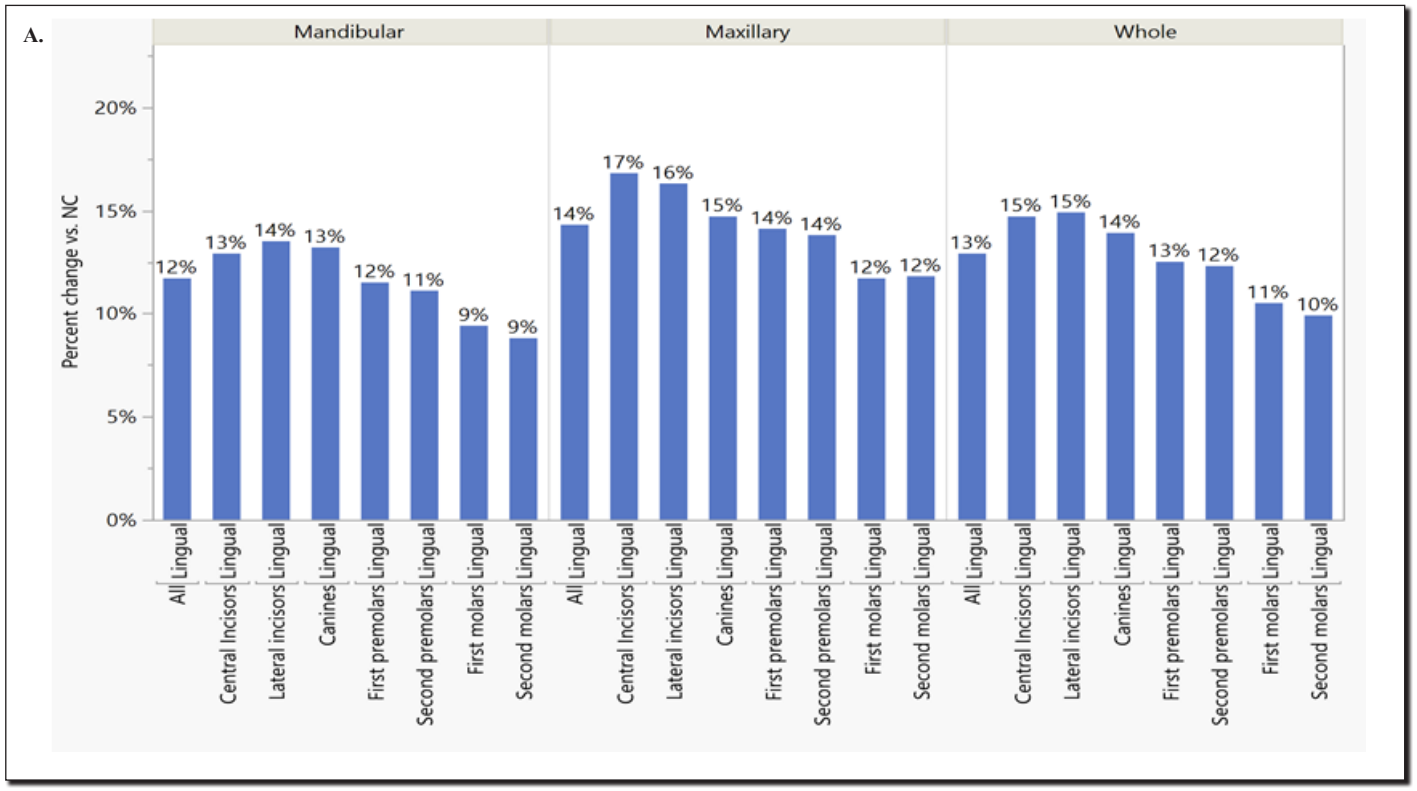
Fig. 3. 4-day plaque studies versus a negative control (A) and positive control (B).

observed equating to a 14% benefit for SnF_2 dentifrice, versus the negative control (P< 0.001) (Fig. 3A). In five 4-day studies assessing SnF_2 dentifrice versus a positive control, a difference in the average 4-day plaque score of -0.15 (95% CI: -0.25, -0.06) was observed equating to an 11% benefit for SnF_2 dentifrice, versus the positive control (P= 0.001) (Fig. 3B). Effect sizes (Cohen's d) equaled 1.29 and 0.68 for comparisons vs. negative control and positive control separately indicating large and moderate effect.

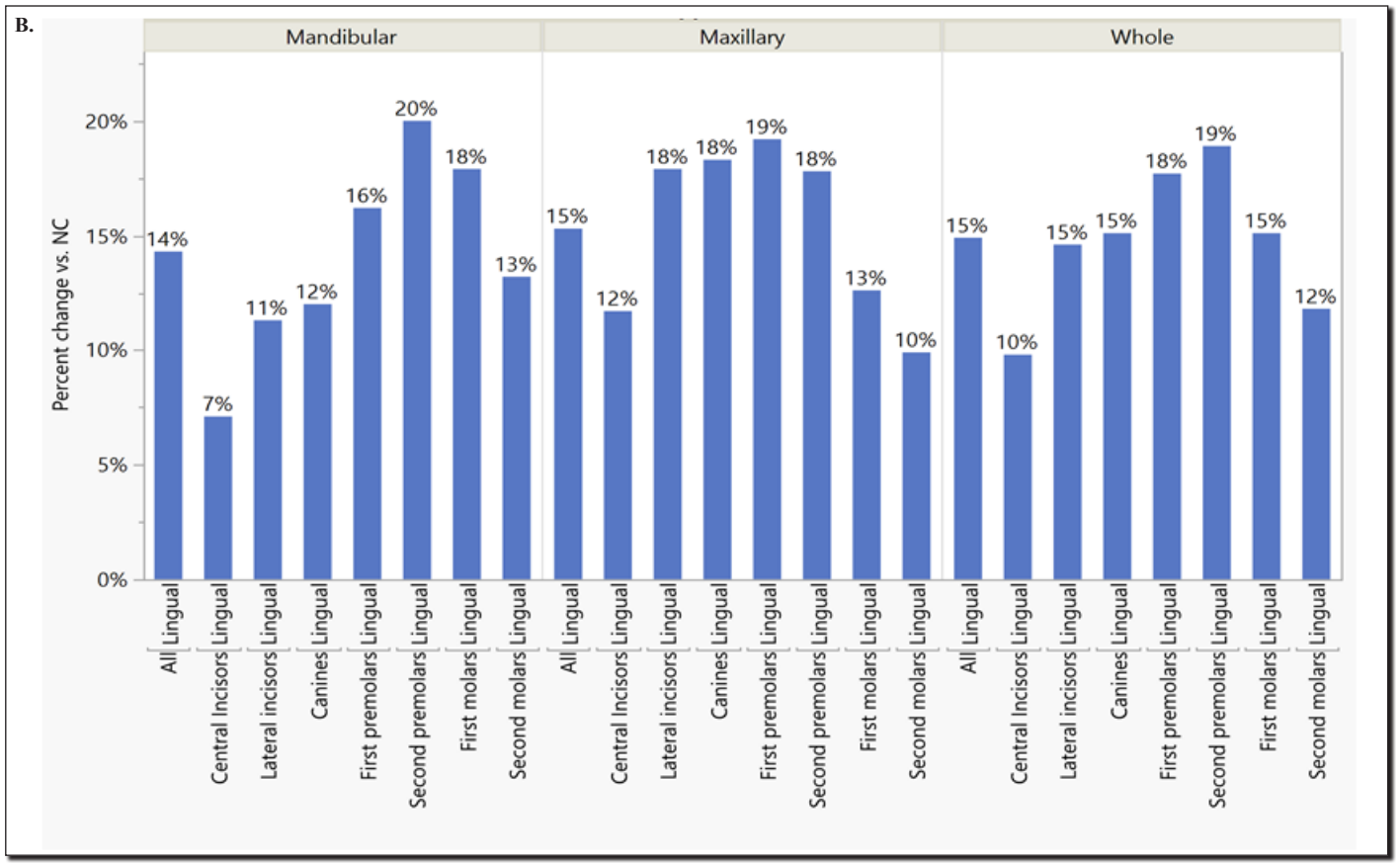
Analysis of plaque reduction by tooth surface and type - The pooled analyses of RCTs comparing SnF_2 dentifrice to a negative control by lingual tooth surface and tooth type are shown in Figs. 4A and B. In longer-term studies, SnF_2 dentifrice resulted in a 13% antiplaque benefit versus the negative control (P< 0.001) for Whole Mouth All Lingual surfaces (Fig. 4A). In 4-day studies, SnF_2 dentifrice resulted in a 15% antiplaque benefit versus the negative control (P< 0.001) for Whole Mouth All Lingual surfaces (Fig. 4B). The antiplaque benefit for SnF_2 dentifrice versus the negative control was observed for lingual surfaces of mandibular and maxillary teeth in both longer-term and 4-day studies (P≤ 0.009) (Figs. 4A and B).

The pooled analyses of RCTs comparing SnF_2 dentifrice to a negative control by buccal tooth surface and tooth type are shown in Figs. 5A and B. In longer-term studies, SnF_2 dentifrice resulted in a 15% antiplaque benefit versus the negative control (P< 0.001) for Whole Mouth All Buccal surfaces (Fig. 5A). In 4-day studies, SnF_2 dentifrice resulted in a 14% antiplaque benefit versus the negative control (P< 0.001) for Whole Mouth All Buccal (unbrushed) surfaces (Fig. 5B). The antiplaque benefit of the SnF_2 dentifrice versus the negative control was observed for buccal surfaces of mandibular and maxillary teeth in both longer-term and 4-day studies (P≤ 0.049) (Figs. 5A and B).

Risk of bias - For all internal bias categories, the risk of bias in individual studies was deemed low. Each study included in these pooled analyses was blinded and randomized. Furthermore, the allocation sequence was unknown until after all participants had been enrolled and assigned to treatment, addressing bias arising from the randomization process. The analyses for each individual study were conducted per the per-protocol population to evaluate the effect of adhering to intervention, addressing bias due to deviations from the intended interventions. Outcomes were available for all, or virtually all participants, addressing bias due to missing outcome data. All trials used valid, reliable outcome measures, and in the case of single-blind studies, the examiners were not aware of the participants' assigned intervention during the trial addressing bias in measurement of the outcome. All studies, both published and unpublished,



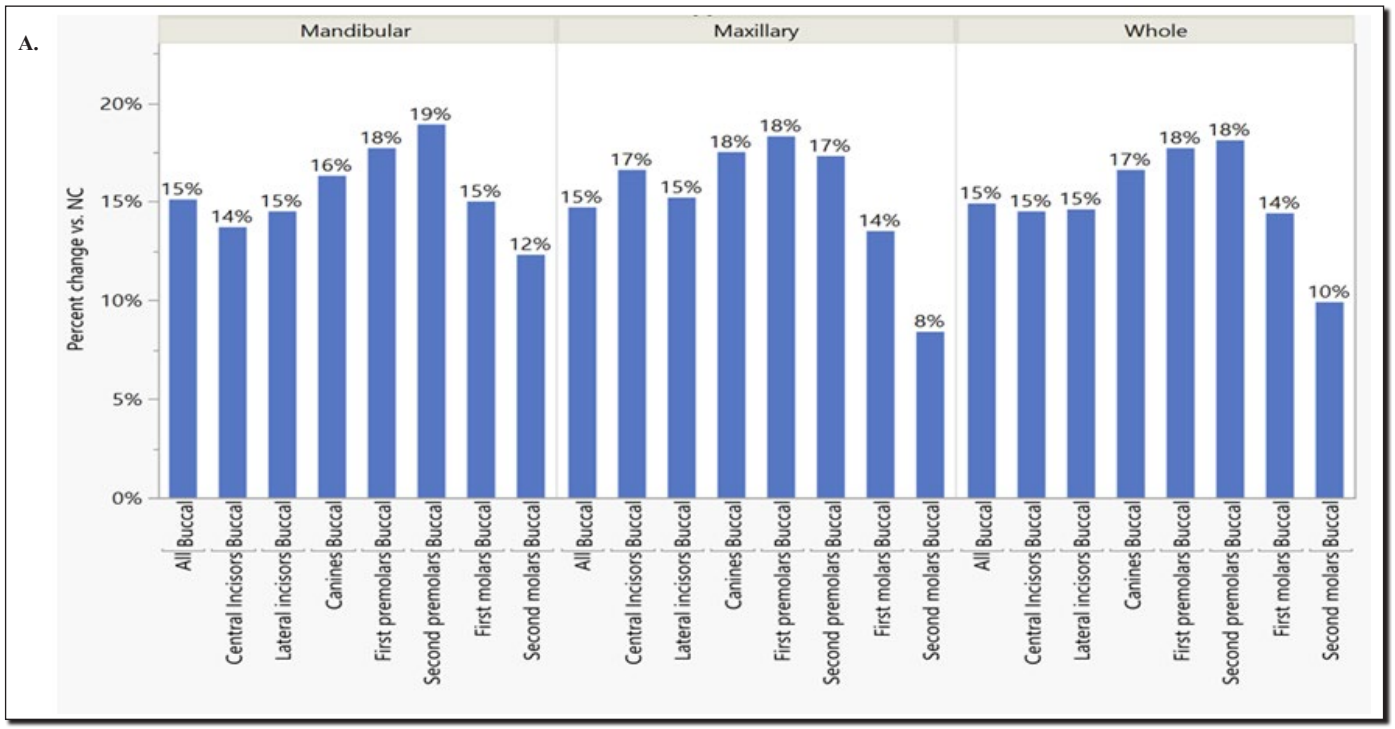
NC=negative control. SnF_2 dentifrice showed a statistically significantly greater percent change in plaque for all tooth types and surfaces versus the control, P≤ 0.009.



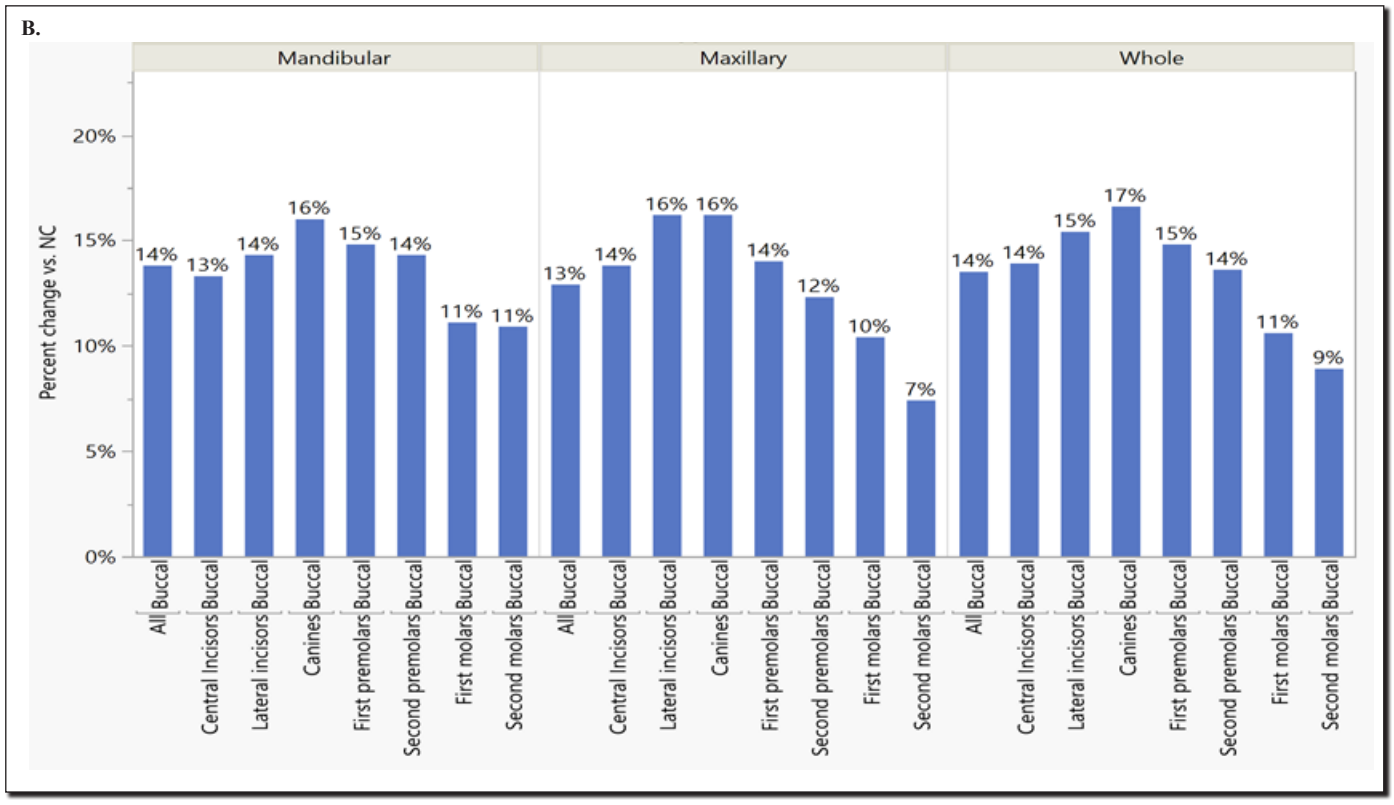
NC=negative control. SnF_2 dentifrice showed a statistically significantly greater percent change in plaque for all tooth types and surfaces versus the control, P≤ 0.001.

Fig. 4. Percent change versus negative control for lingual tooth surfaces by tooth type: Longer-term (A) and 4-day (B) studies.

had a pre-specified analysis plan, with results included regardless of outcome to address bias in the selection of the reported result. The studies in these pooled analyses were all sponsored by the Procter & Gamble Company, a potential source of sys-



NC=negative control. SnF_2 dentifrice showed a statistically significantly greater percent change in plaque for all tooth types and surfaces versus the control, P< 0.049.



NC, negative control. SnF_2 dentifrice showed a statistically significantly greater percent change for all tooth types and surfaces versus the control, P< 0.001.

Fig. 5. Percent change versus negative control for buccal tooth surfaces by tooth type: Longer-term (A) and 4-day (B) studies.

tematic bias. The risk of across-study bias is assuaged in that all studies were randomized, blinded, and controlled and by the large scope of the research involving 44 studies across numerous sites in six countries, supporting the validity and reproducibility of results.

Discussion

The present pooled analyses investigated the short- and longer-term anti-plaque effects of therapeutic bioavailable gluconate chelated 0.454% SnF_2 dentifrices against various controls based on an extensive dataset of randomized controlled

clinical studies with plaque as the primary endpoint in most cases. The significant antiplaque benefit for SnF_2 dentifrice relative to both negative and positive controls was seen consistently in both 4-day and longer-term clinical models, across plaque indices, and by tooth surface and type. The results of the clinical relevance assessments indicate that the difference between the SnF_2 dentifrice and positive and negative controls was potentially clinically relevant.

The 4-day plaque regrowth model was originally introduced as a non-brushing model so that the chemotherapeutic effect of a test product could be evaluated without the interference of mechanical oral hygiene. Over time the model has evolved to a partial brushing model to improve the compliance of the study subjects.[46-51] The model is well-established and used to evaluate the plaque control properties of oral hygiene products. In 4-day plaque studies included in the present pooled analyses, subjects brushed their lingual surfaces and used dentifrice slurry on the buccal surfaces.[46,47] A consistent benefit for SnF_2 dentifrice was observed on both brushed and unbrushed surfaces. Results across all studies demonstrated an antiplaque benefit for SnF_2 dentifrice in buccal sites of 14% and 15% versus the negative control in 4-day and longer-term studies, respectively, and the benefit for lingual sites was 15% and 13% versus the negative control in 4-day and longer-term studies, respectively.

These findings in favor of the SnF_2 dentifrice in the non-brushed buccal surfaces using the 4-day plaque model indicate that the antiplaque benefit for SnF_2 chemistry extends beyond brushing. This is important as most patients do not achieve complete plaque removal with standard toothbrushing.[52] Moreover, many dental professionals are unaware that SnF_2 provides antiplaque benefits via inhibiting regrowth and virulence of plaque beyond brushing,[53] unlike sodium fluoride and sodium monofluorophosphate dentifrice. The antiplaque effect of SnF_2 has been achieved through the mechanism of reducing bacterial metabolic byproducts, lowering salivary bacterial count, reducing bacterial toxins, and shifting the oral microbiome from bacteria associated with disease towards those associated with oral health.[54-57]

Analysis by tooth type has shown plaque reduction across all tooth types in favor of SnF_2 dentifrices. In both 4-day and longer-term studies, smaller plaque reductions in 2nd molars and then 1st molars were observed for both buccal and lingual surfaces. Additionally, in 4-day studies, mandibular incisors exhibited lower plaque reductions on the lingual surfaces. The findings suggest molars in the posterior location of the mouth and mandibular lingual surfaces of incisors are difficult-to-reach sites. These locations are also recognized as gingivitis-prone sites[58] which warrant enhanced care such as incorporating an electric toothbrush as part of the oral care regimen.

In analyses by plaque assessment method, DPIA results on the maxillary and mandibular anterior facial surfaces of teeth were consistent with whole mouth data as captured by TQHPI, RMNPI, and the Silness and Löe Plaque Index.

Prior meta-analyses/pooled analyses have shown an antiplaque effect for SnF_2 dentifrices. The Gunsolley meta-analysis[18] of 6-month studies found statistically significant evidence of an antiplaque benefit for SnF_2 dentifrices. The magnitude of the difference was marginal. However, the author suggested that the efficacy of SnF_2 in reducing gingivitis is mainly due to its alteration of plaque virulence. A 2016 network meta-analysis[59] of RCTs that measured plaque effect using TQHPI showed a greater reduction in plaque scores in favor of SnF_2 dentifrice relative to negative controls. More recently, an analysis by Valkenburg et al[60] provided evidence in favor of SnF_2 or triclosan dentifrice versus sodium fluoride dentifrice for plaque inhibition as determined by the Quigley-Hein Index or DPIA. The Salzer et al[19] paper, which only compared SnF_2 and triclosan dentifrices, suggested that both actives provided gingival health benefit and the differences between the active ingredients were inconclusive. Consistent with the present pooled analysis, a systematic review conducted by Johannsen et al[10] demonstrated an antiplaque benefit for SnF_2 dentifrices versus other dentifrices in both 4-day and longer-term studies. Notably, the Johannsen et al[10] analyses showed substantial heterogeneity, with reductions in plaque ranging from 1.6% to 25.8% depending on the plaque index used and the study duration. Similarly, the Paraskevas & van der Weijden[61] systematic review found evidence of a plaque reduction benefit in favor of SnF_2 dentifrice versus sodium fluoride dentifrice, but the magnitude of the effect was difficult to assess due to high heterogeneity.

There are two aspects of this pooled analysis design that could be considered limitations. First, only a fraction of 4-day plaque studies have been published. This is not due to deficiencies in the model or data, but rather the model has been very stable with key design features and procedures remained the same across the studies. Another perceived limitation is the lack of a systematic review. However, the impact of SnF_2 bioavailability on efficacy is well-known and therefore it was critical to have access to analytical records and antimicrobial performance data as well as subject-level data for the tooth type analysis. These objectives were achieved by using studies from an accessible single database.

The pooled analyses reported here demonstrate consistent, clinically observable benefits for this specific formulation family of SnF_2 dentifrices versus negative and positive controls and include the broadest and largest set of data having three times or more studies than any of the previously published reports. Studies evaluated in these pooled analyses ranged from 4 days to 3 months and plaque was a primary benefit in most studies, whereas many of the previous analyses only included studies 6 months or longer and plaque was often a secondary measure. This indicates that assessing plaque as a primary measure and including studies with assessments as early as 4 days may be a more accurate way to evaluate plaque. These findings have relevance for overall patient care. The family of stabilized SnF_2 dentifrices included in these pooled analyses has been shown to reduce gingivitis through binding to bacterial endotoxins that trigger the inflammatory process, resulting in less virulent plaque, a more balanced oral microbiome, and decreased inflammation and bleeding.[56,62,63] Importantly, relationships have been established between periodontal disease and certain systemic diseases, including cardiovascular disease and diabetes, and periodontal inflammation is a risk factor for the systemic inflammation common to many systemic conditions.[64] A preventive approach to periodontal disease, which includes daily plaque control, has also been shown to increase healthy life years and reduce economic

costs to society in an independent analysis of prevention versus treatments approaches to periodontitis.[3]

Conclusion

The present pooled analyses demonstrated statistically significant plaque inhibition effects of bioavailable SnF_2 dentifrices versus negative and positive controls regardless of clinical model, plaque assessment method, tooth type or tooth surface. As these findings were restricted to a specific bioavailable gluconate chelated SnF_2 dentifrice family, results cannot be generalized to other SnF_2 formulations.

Acknowledgements: To Phyllis Hoke, BA, MEd, for assistance with statistical analysis and Liz Phipps, PhD, CMPP, for assistance with manuscript development.

Disclosure statement: All authors are employees of The Procter & Gamble Company. This work was funded by The Procter & Gamble Company.

Dr. He is a Principal Clinical Scientist, Dr. Zou is a Senior Statistician, Mr. DiGennaro is a Director and Dr. Biesbrock is a Senior Director and Lead Life Scientist at The Procter & Gamble Company, Mason, Ohio, USA.

References

1. FDI World Dental Federation. The Challenge of Oral Disease - A Call for Global Action. The Oral Health Atlas, 2nd ed. Geneva: FDI World Dental Federation. 2015.
2. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, Listl S, Celeste RK, Guarnizo-Herreño CC, Kearns C, Benzian H, Allison P, Watt RG. Oral diseases: A global public health challenge. *Lancet* 2019;394:249-260.
3. Bishop C. Time to take gum disease seriously: The societal and economic impact of periodontitis - The Economist Intelligence Unit (EIU). Available at: https://eiuperspectives.economist.com/sites/default/files/eiu-efp-oralb-gum-disease.pdf.
4. van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. *J Clin Periodontol* 2005;32(Suppl 6):214-228.
5. Deinzer R, Ebel S, Blattermann H, Weik U, Margraf-Stiksrud J. Toothbrushing: To the best of one's abilities is possibly not good enough. *BMC Oral Health* 2018;18:167.
6. Fleming EB, Nguyen D, Afful J, Carroll MD, Woods PD. Prevalence of daily flossing among adults by selected risk factors for periodontal disease-United States, 2011-2014. *J Periodontol* 2018;89:933-939.
7. Ng E, Lim LP. An overview of different interdental cleaning aids and their effectiveness. *Dent J (Basel)* 2019;7.
8. Huang S, He T, Yue F, Xu X, Wang L, Zhu P, Teng F, Sun Z, Liu X, Jing G, Su X, Jin L, Liu J, Xu J. Longitudinal multi-omics and microbiome meta-analysis identify an asymptomatic gingival state that links gingivitis, periodontitis, and aging. *mBio* 2021;12:e03281-20.
9. Baehni PC, Takeuchi Y. Anti-plaque agents in the prevention of biofilm-associated oral diseases. *Oral Dis* 2003;9(Suppl 1):23-29.
10. Johannsen A, Emilson CG, Johannsen G, Konradsson K, Lingstrom P, Ramberg P. Effects of stabilized stannous fluoride dentifrice on dental calculus, dental plaque, gingivitis, halitosis and stain: A systematic review. *Heliyon* 2019;5:e02850.
11. Biesbrock A, He T, DiGennaro J, Zou Y, Ramsey D, Garcia-Godoy F. The effects of bioavailable gluconate chelated stannous fluoride dentifrice on gingival bleeding: Meta-analysis of eighteen randomized controlled trials. *J Clin Periodontol* 2019;46:1205-1216.
12. West NX, He T, Zou Y, DiGennaro J, Biesbrock A, Davies M. Bioavailable gluconate chelated stannous fluoride toothpaste meta-analyses: Effects on dentine hypersensitivity and enamel erosion. *J Dent* 2021;105:103566.
13. Konradsson K, Lingström P, Emilson CG, Johannsen G, Ramberg P, Johannsen A. Stabilized stannous fluoride dentifrice in relation to dental caries, dental erosion and dentin hypersensitivity: A systematic review. *Am J Dent* 2020;33:95-105.
14. Baig A, He T. A novel dentifrice technology for advanced oral health protection: A review of technical and clinical data. *Compend Contin Educ Dent* 2005;26:4-11.
15. Tinanoff N. Progress regarding the use of stannous fluoride in clinical dentistry. *J Clin Dent* 1995;6(Spec No):37-40.
16. White DJ. A "return" to stannous fluoride dentifrices. *J Clin Dent* 1995;6(Spec No):29-36.
17. He T, Nachnani S, Lee S, Zou Y, Grender J, Farrell S, Sagel P, Biesbrock AR. The relative clinical efficacy of three 0.454% stannous fluoride dentifrices for the treatment of gingivitis over 3 months. *Am J Dent* 2020;33:218-224.
18. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *J Am Dent Assoc* 2006;137:1649-1657.
19. Salzer S, Slot DE, Dorfer CE, Van der Weijden GA. Comparison of triclosan and stannous fluoride dentifrices on parameters of gingival inflammation and plaque scores: A systematic review and meta-analysis. *Int J Dent Hyg* 2015;13:1-17.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009;6:e1000097.
21. Quigley GA, Hein JW. Comparative cleansing efficiency of manual and power brushing. *J Am Dent Assoc* 1962;65:26-29.
22. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of victamine C. *J Periodontol* 1970;41:41-43.
23. Rustogi KN, Curtis JP, Volpe AR, Kemp JH, McCool JJ, Korn LR. Refinement of the Modified Navy Plaque Index to increase plaque scoring efficiency in gumline and interproximal tooth areas. *J Clin Dent* 1992;3:C9-C12.
24. Sagel PA, Lapujade PG, Miller JM, Sunberg RJ. Objective quantification of plaque using digital image analysis. *Monogr Oral Sci* 2000;17:130-143.
25. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condition. *Acta Odontol Scand* 1964;22:121-135.
26. Higgins JPT, Sterne JAC, Savovic J, Page MJ, Hrobjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials, in: Chandler J, McKenzie J, Boutron I, Welch V. Cochrane Methods. Cochrane Database of Systematic Reviews 2016, https://doi.org/10.1002/ 14651858.CD201601. Issue 10 (Suppl 1), https://training.cochrane.org/h andbook/current/chapter-23.
27. Page P. Beyond statistical significance: Clinical interpretation of rehabilitation research literature. *Int J Sports Phys Ther* 2014;9:726-736.
28. R Development Core Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN3-900051-07-0. https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing, 2015 (accessed 17 May 2020)
29. Viechtbauer W. Conducting meta-analyses in R with the metaphor package. *J Stat Softw* 2010;36:1-48. https://doi.org/10.18637/jss.v036.i03
30. Beiswanger BB, Doyle PM, Jackson RD, Mallatt ME, Mau Ms, Bollmer BW, Crisanti MM, Guay CB, Lanzalaco AC, Lukacovic MF, Majeti S, McClanahan SF. The clinical effect of dentifrices containing stabilized stannous fluoride on plaque formation and gingivitis - A six-month study with ad libitum brushing. *J Clin Dent* 1995;6(Spec No):46-53.
31. McClanahan SF, Beiswanger BB, Bartizek RD, Lanzalaco AC, Bacca L, White DJ. A comparison of stabilized stannous fluoride dentifrice and triclosan/copolymer dentifrice for efficacy in the reduction of gingivitis and gingival bleeding: Six-month clinical results. *J Clin Dent* 1997;8(2 Spec No):39-45.
32. Mankodi S, Bartizek RD, Winston JL, Biesbrock AR, McClanahan SF, He T. Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice. *J Clin Periodontol* 2005;32:75-80.
33. Mallatt M, Mankodi S, Bauroth K, Bsoul SA, Bartizek RD, He T. A controlled 6-month clinical trial to study the effects of a stannous fluoride dentifrice on gingivitis. *J Clin Periodontol* 2007;34:762-767.
34. Gerlach R, Sagel P, Winston JL, Garcia-Godoy C, Garcia-Godoy F. Randomized controlled trial evaluating oral health effects of two-step hygiene. *J Dent Res* 2016;96(Spec Iss A):Abstr 91.
35. Papas AS, Singh ML, Magnuson B, Tzavaras E, Cimmino J, Anastasia M, Gerlach RW. Safety and effectiveness of two-step paste/gel sequence with medication hyposalivation. *J Dent Res* 2015;94(Spec Iss A):Abstr 3454.
36. Garcia-Godoy C, Flores KL, Anastasia MK, Zou Y, Gurich Y. Reduction of overnight plaque with use of two-step oral hygiene system. *J Dent Res* 2019;98(Spec Iss A): Abstr 3268.
37. Nachnani S, He T, Peters J, Eusebio R, Lee S, Farrell S. Plaque effects of bioavailable SnF_2 dentifrice: Results from a 3-month trial. *J Dent Res* 2019;98(Spec Iss A):Abstr 2326.
38. Amini P, He T, Peters J, Farrell S. Clinical plaque and gingivitis effects of bioavailable SnF_2 dentifrice. *J Dent Res* 2020;99(Spec Iss A):Abstr 3067.
39. He T, Mazor S, Zou Y, Grender J, Farrell S, Sagel P, Biesbrock AR, Timm H, Zini A. Randomized clinical trial assessing anti-gingivitis efficacy of two stannous fluoride dentifrices and zinc/arginine dentifrice. *Am J Dent* 2021;34:110-115.

40. Klukowska M, Zou Y, Ponce D, Amini P. Rapid antigingivitis efficacy of a novel stannous fluoride dentrifice: Results from a 12-week randomized controlled clinical trial. *Compend Contin Educ Dent* 2021;42:e5-e9.
41. Barker ML, Gerlach RW, Sagel P. Plaque imaging comparison of two-step SnF_2/H_2O_2 dentifrices versus triclosan dentifrice. *J Dent Res* 2015;94(Spec Iss A):Abstr 294.
42. Bretz WA, Corby PM, Corby AL, Moreira A, Barker ML, Gerlach RW, Biesbrock AR. Comparative overnight plaque response to therapeutic dentifrices in twins. *J Dent Res* 90(Spec Iss A):Abstr 1319.
43. He T, Barker ML, Biesbrock AR, Eynon H, Milleman JL, Milleman KR, Putt MS, Wintergerst AM. Digital plaque imaging evaluation of a stabilized stannous fluoride dentifrice compared with a triclosan/copolymer dentifrice. *Am J Dent* 2013;26:303-306.
44. White DJ, Barker ML, Miner M, White DJ, Sharma N, Qaqish J. Anti-plaque efficacy of stannous fluoride dentifrice relative to triclosan control. *J Dent Res* 2013;92(Spec Iss A):Abstr 941.
45. Friesen LR, Goyal CR, Qaqish JG, He T, Eusebio R, Zsiska M, Farmer T, Schneiderman E. Comparative antiplaque effect of two antimicrobial dentifrices: Laboratory and clinical evaluations. *J Clin Dent* 2017;28(4 Spec No B):B6-B11.
46. Barker ML, Cheng R, Dunavent JM, Biesbrock AR, He T. Meta-analysis of clinical anti-plaque effectiveness for 0.454% stannous fluoride dentifrices. *J Dent Res* 2011;90 (Spec Iss A):Abstr 1318.
47. Cronin M, He T, Eynon H, Miner M, Barker ML, Schadt M. Study to assess the anti-plaque efficacy of two marketed dentifrices. *J Dent Res* 2012;91(Spec Iss A):Abstrt 1447.
48. Arweiler NB, Boehnke N, Sculean A, Hellwig E, Auschill TM. Differences in efficacy of two commercial 0.2% chlorhexidine mouthrinse solutions: A 4-day plaque re-growth study. *J Clin Periodontol* 2006; 33:334-339.
49. Moran J, Addy M, Kohut B, Hovliaras CA, Newcombe RG. Efficacy of mouthrinses in inhibiting the development of supragingival plaque over a 4-day period of no oral hygiene. *J Periodontol* 1994;65:904-907.
50. Addy M, Willis L, Moran J. Effect of toothpaste rinses compared with chlorhexidine on plaque formation during a 4-day period. *J Clin Periodontol* 1983;10:89-99.
51. He T, Dunavent J, Booker S, Fiedler SK, Baker RA. Anti-plaque effects of various dentifrices using a 4-day plaque model. *J Dent Res* 2009;88(Spec Iss A):722.
52. Slot DE, Wiggelinkhuizen L, Rosema NAM, Van der Weijden GA. The efficacy of manual toothbrushes following a brushing exercise: A systematic review. *Int J Dent Hyg* 2012;10:187-197.
53. International Federation of Dental Hygienists. 2019 Toothpaste Survey. Retrieved from http://www.ifdh.org/ifdh-2019-toothpaste-survey.html on 6 July, 2022.
54. Addy M, Greenman J, Renton-Harper P, Newcombe R, Doherty F. Studies on stannous fluoride toothpaste and gel (2). Effects on salivary bacterial counts and plaque regrowth in vivo. *J Clin Periodontol* 1997;24:86-91.
55. Ramji N, Baig A, He T, Lawless MA, Saletta L, Suszcynsky-Meister E, Coggan J. Sustained antibacterial actions of a new stabilized stannous fluoride dentifrice containing sodium hexametaphosphate. *Compend Contin Educ Dent* 2005;26:19-28.
56. He T, Huang S, Yue F, Wang L, Liu J, Xu J. A randomized, controlled comparison of a stannous-containing dentifrice for reducing gingival bleeding and balancing the oral microbiome relative to a positive control. *Am J Dent* 2021;34:222-227.
57. Kruse AB, Schlueter N, Kortmann VK, Frese C, Anderson A, Wittmer A, Hellwig E, Vach K, Al-Ahmad A. Long-term use of oral hygiene products containing stannous and fluoride ions: Effect on viable salivary bacteria. *Antibiotics (Basel)* 2021;10:481.
58. Archila L, Bartizek RD, Winston JL, Biesbrock AR, McClanahan MF, He T. The comparative efficacy of stabilized stannous fluoride/sodium hexametaphosphate dentifrice and sodium fluoride/triclosan/copolymer dentifrice for the control of gingivitis: A six-month randomized clinical study. *J Periodontol* 2004;75:1592-1599.
59. Escribano M, Figuero E, Martín C, Tobías A, Serrano J, Roldán S, Herrera D. Efficacy of adjunctive anti-plaque chemical agents: A systematic review and network meta-analyses of the Turesky modification of the Quigley and Hein plaque index. *J Clin Periodontol* 2016;43:1059-1073.
60. Valkenburg C, Else Slot D, Van der Weijden GF. What is the effect of active ingredients in dentifrice on inhibiting the regrowth of overnight plaque? A systematic review. *Int J Dent Hyg* 2020;18:128-141.
61. Paraskevas S, van der Weijden GA. A review of the effects of stannous fluoride on gingivitis. *J Clin Periodontol* 2006;33:1-13.
62. He T, Eusebio R, Goyal CR, Qaqish JG. Assessment of the effects of a novel stabilized stannous fluoride dentifrice on gingivitis in a two-month positive-controlled clinical study. *J Clin Dent* 2017;28:B12-B16.
63. Klukowska M, Haught JC, Xie S, Circello B, Tansky CS, Khambe D, Huggins T, White DJ. Clinical effects of stabilized stannous fluoride dentifrice in reducing plaque microbial virulence. I: Microbiological and receptor cell findings. *J Clin Dent* 2017;28:16-26.
64. Paul O, Arora P, Mayer M, Chatterjee S. Inflammation in periodontal disease: Possible link to vascular disease. *Front Physiol* 2020;11:609614.