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3 **Root Coverage procedures improve patient aesthetics. A Systematic Review and Bayesian**  
4 **network meta-analysis.**  
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54 **Keywords:** gingival recession, aesthetics, systematic review, meta-analysis.  
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56 **Running Title:** Aesthetics after root coverage.  
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**ABSTRACT**

**Background:** The aim of this study was to perform a systematic review (SR) of randomized controlled trials (RCTs) to explore if periodontal plastic surgery procedures for the treatment of single and multiple gingival recessions (Rec) may improve aesthetics at patient and professional levels.

**Material and Methods:** In order to combine evidence from direct and indirect comparisons by different trials a Bayesian network meta-analysis (BNM) was planned. A literature search on PubMed, Cochrane libraries, EMBASE, and hand-searched journals until January 2015 was conducted to identify RCTs presenting aesthetic outcomes after root coverage using standardized evaluations at patient and professional level.

**Results:** A total of 16 RCTs were selected in the SR; 3 RCTs presenting professional aesthetic evaluation with Root coverage Aesthetic Score (RES) and 3 showing final self-perception using the Visual Analogue Scale (VAS Est) could be included in a BNM model. Coronally Advanced Flap plus Connective Tissue Graft (CAF+CTG) and CAF+Acellular Dermal Matrix (ADM) and Autologous Fibroblasts (AF) were associated with the best RES outcomes (best probability = 24% and 64%, respectively), while CAF+CTG and CAF+CTG+Enamel matrix Derivatives (EMD) obtained highest values of VAS Est score (best probability = 44% and 26%, respectively).

**Conclusions:** Periodontal Plastic Surgery (PPS) techniques applying grafts underneath CAF with or without the adding of EMD are associated with improved aesthetics assessed by final patient perception and RES as professional evaluation system.

## CLINICAL RELEVANCE

### *Scientific rationale for the study:*

To compare, using a Bayesian network meta-analysis, the efficacy of periodontal plastic surgery procedures to improve aesthetics as assessed by professional and patient scores.

### *Principal findings:*

Coronally Advanced Flap plus Connective Tissue Graft (CAF+CTG) and CAF plus Acellular Dermal Matrix (ADM) and Autologous Fibroblasts (AF) were associated with the highest professional outcomes rated by means of Root Coverage Aesthetics Score (RES). CAF+CTG and CAF+CTG plus Enamel Matrix Derivatives (EMD) obtained highest values in term of patient satisfaction rated by Visual Analogue Scale (VAS est).

### *Practical implications:*

Grafting underneath the Coronally Advanced Flap with or without the adding of Enamel Matrix Derivatives is associated with highest aesthetic outcomes at professional and patient level.

**Conflict of Interest:** The authors certify that there is no conflict of interest concerning the contents of the study.

**Source of Funding:** The study was self founded by authors.

## INTRODUCTION

Aesthetic concern is a primary indication for treatment of gingival recession (AAP 1996). In the last decade a large amount of data have shown that different procedures are effective in obtaining root coverage. Randomized clinical trials (RCTs) and systematic reviews (SRs) showed that combination of coronally advanced flap and connective tissue graft (CAF+CTG) is associated with the highest probability to achieve complete root coverage (CRC) for single gingival recession with no loss of interproximal attachment (Cairo et al. 2008; Chambrone et al. 2008, 2010, Cortellini et al. 2009; Cairo et al. 2014, Pini Prato et al. 2014, Chambrone & Tatakis 2015). Emerging data also showed similar clinical outcomes at single gingival recession with loss of interproximal attachment (Cairo et al. 2012; Cairo et al. 2015). Furthermore, the efficacy of surgical procedures in cases of multiple gingival recessions is less investigated (Graziani et al. 2014). On the other hand, a recent SR regarding untreated recession defects in subjects with good oral hygiene shows high probability of progressing during long-term follow-up (Chambrone & Tatakis 2016)

Recently, some methods to evaluate aesthetic outcomes after root coverage have been suggested in order to standardize the qualitative assessment of healed soft tissue over root surface (Kerner et al. 2009, Cairo et al. 2009). In addition, the collection of patient-related outcomes including aesthetics satisfaction has been recommended for clinical trials on root coverage procedures (Roccuzzo et al. 2002; Chambrone et al. 2010, Tonetti et al. 2014).

Previous systematic reviews in periodontal plastic surgery (Cairo et al. 2008, Cairo et al. 2014) failed to perform meta-analysis by means of conventional systems concerning aesthetic outcomes due to the presence of few and heterogeneous data among studies. Network meta-analysis (also called the Mixed-Treatment Comparisons) (Lumley 2002) was developed as a new approach to

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3 meta-analysis. Different from standard meta-analytical techniques, allowing single separate pair-  
4 wise, head-to-head, comparisons, NM is able to combine evidence from both direct and indirect  
5 comparisons from different trials in a unique network of treatments (Buti et al. 2011). In presence  
6 of several treatments for the same condition, lack of all possible comparisons is frequently  
7 recognised in the body of literature and only indirect inference is possible on the comparisons that  
8 are not informed by data. However, the use of indirect comparison methods and the results of the  
9 analysis must be interpreted with caution. When planning a NM, it is important to assess patient and  
10 study characteristics among studies that compare pairs of treatments to understand if distribution of  
11 effect modifiers such as age, gender, disease severity, consistency of treatments in intervention  
12 trials is similar across studies (Hutton et al. 2015).  
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27 The purpose of this study was to conduct a systematic review of RCTs to explore if root coverage  
28 procedures are effective to improve aesthetics assessed by professional evaluation system and final  
29 patient perception. A Bayesian Network Meta-analysis (BNM) model has been considered in order  
30 to summarize quantitative data from included RCTs.  
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## 38 MATERIAL AND METHODS

### 39 Protocol development and Eligibility criteria

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43 A detailed protocol was reported according to the PRISMA (Preferred Reporting Items Systematic  
44 review and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews  
45 Incorporating Network Meta-analyses of Health Care Interventions (Liberati et al. 2009; Moher et  
46 al. 2009; Hutton et al. 2015) (Fig 1). The focused question of this systematic review was “*Is*  
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*periodontal plastic surgery for root coverage effective to improve aesthetics at patient and/or*

operator level?" Only RCTs in English language in the field of periodontal plastic surgery and evaluating aesthetic outcomes with standardized procedures were included.

### Study selection

The criteria for considering studies for this review were organized by the PICO method (Glossary of Evidence-Based Terms 2007) and were as follows:

(P) Type of participants: patients with a clinical diagnosis of localized or multiple gingival recessions. Studies involving only heavy smokers ( $\geq 10$  cigarettes/day) were not enclosed in the SR.

(I) Type of interventions: any type of surgical treatment including possible combinations for treatment of localized or multiple gingival recession defects.

(C) Comparison between interventions: any type of possible comparison between surgical treatments for root coverage, excluding variations of the same technique, with at least 6 months of follow-up.

(O) Type of outcome measures:

Primary outcome was aesthetic assessment of root coverage outcomes using a well-defined patient evaluation and/or a standardized clinical assessment. Aesthetic evaluations using empiric or unclear approaches were not considered.

Studies regarding single and multiple gingival recessions were evaluated separately. When RCTs covering the treatment of both single and multiple recessions were retrieved, these were considered in the group of single recession treatment since the used surgical procedure was originally designed for single defects but extended also to multiple recessions. Further information is presented in Supporting Experimental Procedures, Methods S1-Study selection.

### Information sources and Search

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3 RTCs dealing on root coverage procedures were selected up to January 2016. Details of search were  
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5 presented in Supporting Experimental Procedures, Methods S2-Information sources and Search.  
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10 **Data collection process/ Data items** (Supporting Experimental Procedures, Methods S3-Data  
11  
12 collection process)  
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16 **Risk of bias in individual studies** (Supporting Experimental Procedures, Methods S4-Risk of bias  
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18 in individual studies)  
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23 **Outcome measures**  
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27 *Primary outcome:* aesthetic assessment of root coverage outcomes at patient level using a well-  
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29 defined patient evaluation and/or a standardized clinical assessment.  
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32 *Secondary outcome:* professional evaluation of aesthetic outcomes using standardized approaches.  
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36 Aesthetic evaluations using empiric or unclear approaches were not considered. In order to reduce  
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38 the possible source of heterogeneity, only standardized score systems to evaluate aesthetics used in  
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40 at least 3 different studies were considered for quantitative data analysis.  
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45 **Bayesian network meta-analysis (BNM)**  
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49 It was planned a priori to create a network of RCTs involving single recessions and single plus  
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51 multiple recessions (meaning studies treating both single and multiple recessions) while studies  
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53 involving surgical techniques specifically aimed at treating multiple recessions only were  
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55 considered separately.  
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3 Outcomes along with respective standard deviations were extracted from each primary study and  
4 expressed in percentage (%). Difference between treatments was calculated for each comparison  
5 within individual studies. For split-mouth studies, when standard deviation of the mean difference  
6 was not reported, it was calculated by individual patient data (IPD) if available. When several time  
7 point follow-up measures longer than 6 months were reported for the same sample in the same or  
8 different studies, the early report was selected to retrieve information regarding aesthetic outcomes,  
9 even if also the long-term follow-up was checked to retrieve possible additional outcomes.  
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20 A BNM model was then constructed for each of the outcome variables allowing for the inclusion of  
21 all the possible treatment comparisons. Direct comparisons of treatments as well as indirect  
22 comparisons were analysed in the same framework. Information from direct and indirect evidence  
23 can be combined in a NM only in the case that each treatment/trial is part of a connected network  
24 (i.e each trial shares at least a common comparator treatment). The description of the method and  
25 model specification details is presented in Supporting Experimental Procedures, Methods S5,  
26 Bayesian network meta-analysis.  
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## 38 RESULTS

39 The electronic searches provided a total of 47 abstracts published from May 2013 until January  
40 2016. Subsequently, after full-text reading, 9 articles were selected. By merging these 9 articles  
41 with the references of the previous SRs (Cairo et al. 2014; Graziani et al. 2014) a total of 18 articles  
42 was obtained. At this time, two articles were excluded since a long-term study (McGuire et al.  
43 2012; Cairo et al. 2015) of a previously published short-term trials (McGuire & Nunn 2003; Cairo  
44 et al. 2012). Finally, 16 RCTs met inclusion criteria (Table 1). In one case (Aroca et al. 2013), the  
45 contact of the authors provided further information regarding outcomes variables. The PRISMA  
46 flow chart of the screening and selection process is presented in fig. 1. Rejected studies at this stage  
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3 and rationale for rejection are listed in Supporting Information, Data S1, Rejected studies and  
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5 Appendix S1, references excluded studies.  
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## 9 10 **RESULTS OF THE ANALYSIS**

### 11 **Study characteristics and Risk of bias within studies (see supporting information, Data S2)**

#### 12 13 14 15 16 **Results of the analysis**

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18 Among the applied scoring methods to assess aesthetic outcomes, only VAS Est at patient level and  
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20 RES at professional level were used in at least 3 different studies to be considered for inclusion in a  
21  
22 BNM model. Regarding the two clusters of studies considered (single plus single/multiple  
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24 recessions (S/M Rec) treatment and multiple recessions (MRec) only, VAS Est was applied in 5  
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26 RCTs on S/M Rec (Cairo et al. 2012; Zucchelli et al. 2012; Roman et al. 2013; Salhi et al. 2014;  
27  
28 Zuhr et al. 2014), but data for meta-analysis were reported in 4 RCTs (Cairo et al. 2012; Zucchelli  
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30 et al. 2012; Roman et al. 2013; Zuhr et al. 2014). Only 2 RCTs on MRec applying VAS Est were  
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32 available (Aroca et al. 2013; Zucchelli et al. 2014).  
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36 RES was applied in 5 RCTs regarding S/M Rec (Jhaveri et al. 2000; Cairo et al. 2012; Roman et al.  
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38 2013; Zuhr et al. 2014; Milinkovic et al. 2015) and in 2 RCTs on MRec (Ahmedbeyli et al. 2014;  
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40 Ozenci et al. 2015). The study by Milinkovic et al. 2015 could not be included in the quantitative  
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42 data analysis for S/M Rec group as the statistical tests performed in the original paper were not  
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44 adjusted for the split-mouth design and did not take into account the within-patient correlation. The  
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46 studies available for the MRec group were only 2 (Ahmedbeyli et al. 2014 and Ozenci et al. 2015),  
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48 each one testing a different treatment comparison. Therefore no quantitative data analysis was  
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50 performed.  
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3 Therefore a BNM regarding VAS Est for S/M Rec and a BNM regarding were performed. Studies  
4 included in the BNM models are presented in table 2. The results of the analysis are then reported in  
5 table 3 and presented separately for VAS Est and RES.  
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### 10 11 *Network Geometry*

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13 Two different network geometries were used in order to describe the architecture of evidence for  
14 each of the outcome variables (VAS Est and RES). Network graphs are reported in Fig. 2. Both the  
15 network identified CAF+CTG as the reference treatment. Only 1 RCT was available for each direct  
16 comparison  
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### 23 **VAS Est**

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27 Data from 3 studies included in this systematic review were available for the NM for the  
28 VAS Est outcome variable regarding the treatment of S/M Rec:  
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32 • Zucchelli et al. (2010) considered the comparison between CAF+CTG (test) vs.  
33 LPF (control). The mean VAS Est was  $91.2 \pm 9.3$  for the test group while  $89.6 \pm 7.9$   
34 for the control group. Individual patient data (IPD) available in the paper were re-  
35 analysed to obtain mean difference for VAS Est.  
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- 43 • Cairo et al. (2012) considered the comparison between CAF+CTG (test) vs. CAF  
44 (control). The mean VAS Est was  $80.3 \pm 15$  for the test group while  $75.0 \pm 14.5$  for  
45 the control group. Individual patient data (IPD) were provided by the author and re-  
46 analysed to obtain mean difference for VAS Est.  
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- 53 • Roman et al. (2013) considered the comparison between CAF+CTG+EMD vs.  
54 CAF+CTG. The mean VAS Est was  $87.0 \pm 16$  for the test group while  $89.5 \pm 15$  for  
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3 the control group. Average data from each treatment group available in the paper  
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5 were re-analysed to obtain mean difference for VAS Est.  
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11 The final mean VAS Est considering the 3 studies enclosed in the BNM was 85,4.  
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16 The study by Zuhr et al. (2013) was similarly not included in the present BN for the reasons  
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18 presented above. The mean VAS est for the TT+CTG group was  $9.2 \pm 1.4$  while  $9.1 \pm 1.1$  in the  
19  
20 CAF+EMD group considering a 0 to 10 VAS.  
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25 The treatment alternatives considered for the analysis were 4:

- 26 • CAF
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- 28 • CAF+CTG
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- 30 • CAF+CTG+EMD
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- 32 • LPF
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36 With 4 treatment options, a total of 6 comparisons were possible.

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38 Three direct comparisons were based on data from RCTs:

- 39 • CAF+CTG vs. LPF 1 RCT (50 Patients)
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- 41 • CAF+CTG vs. CAF 1 RCT (29 Patients)
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- 43 • CAF+CTG vs. CAF+CTG+EMD 1 RCT (42 Patients)
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48 Three comparisons were never directly tested in RCTs:

- 49 • LPF vs. CAF
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- 51 • LPF vs. CAF+CTG+EMD
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- 53 • CAF vs. CAF+CTG+EMD
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3 When compared to CAF alone, the greatest mean differences for VAS Est were achieved by  
4 the combined CAF+CTG treatment (-5.42, 90%CrI: [-14.56; 3.73]), and then by LPF (-3.79,  
5 90%CrI: [-13.78; 6.16]) and CAF+CTG+EMD (-2.93, 90%CrI: [-9.08; 14.86]). The CAF+CTG  
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7 combination resulted to be slightly better than CAF+CTG+EMD (-2.49, 90%CrI: [-10.31; 5.29])  
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9 and than LPF (-1.63, 90%CrI: [-5.65; 2.35]), but the estimated difference did not result to be either  
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11 statistically or clinically relevant.  
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16 The BNM model produced estimates also on the LPF vs. CAF+CTG+EMD, but the  
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18 estimated difference did not result to be either statistically or clinically significant.  
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21 All pair-wise comparisons for VAS Est are reported in Table 3.

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23 The *Ranking* of treatments by effectiveness was the following: 1. CAF+CTG (posterior  
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25 median rank = 1.71); 2. LPF (2.45); 3. CAF+CTG+EMD (2.61); 4. CAF (3.23) (Table 4, Fig. 4-  
26  
27 additional material).  
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30 The surgical procedures with the highest probability (Pr) of being the *Best* treatments were  
31  
32 the combined CAF+CTG treatment (Pr = 44%) and CAF+CTG+EMD (Pr = 26%) (Table 4, Fig. 4-  
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34 additional material). The largest SUCRA was obtained for CAF+CTG (0.75). The performance of  
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36 LPF and CAF+CTG+EMD was similar (SUCRA= 0.52 and 0.46, respectively). (Fig. 3)  
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## 40 RES

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45 Data from 3 out of the 14 studies included in this systematic review were available for the  
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47 BNM for the RES outcome variable regarding the treatment of S/M Rec:

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49 • Jhaveri et al. (2010) considered the comparison between CAF+ADM with AF (test)  
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51 vs CAF+CTG. The authors reported  $8.1 \pm 2.3$  of mean final RES for test group while  
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53  $7.9 \pm 1.3$  for the control group. Individual patient data (IPD) available in the paper  
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55 were re-analysed to obtain mean difference for RES.  
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- Cairo et al. (2012) considered the comparison between CAF+CTG (test) vs. CAF (control). The mean RES was  $7.6 \pm 1.7$  for the test group while  $6.7 \pm 1.5$  for the control group. Individual patient data (IPD) were provided by the author and re-analysed to obtain mean difference for RES.
  - Roman et al. (2013) considered the comparison between CAF+CTG+EMD (test) vs. CAF+CTG (control). The mean RES was  $8.6 \pm 1.5$  for the test group while  $9.0 \pm 1.1$  for the control group. Average data from each treatment group available in the paper were re-analysed to obtain mean difference for RES.

23 The final mean RES score considering the 3 studies enclosed in the BNM was 7,9.

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27 The study by Zuhr et al. (2013), investigating tunnel technique with connective tissue graft (TT+CTG) and coronally advanced flap with enamel matrix derivative (CAF+EMD), could not be included in the Network Meta-analysis model for RES, as neither these surgical procedures were tested in the trials included in the network. Zuhr et al. reported mean RES of  $9.1 \pm 0.8$  for TT+CTG group and  $6.9 \pm 2.3$  for CAF+EMD group.

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40 The treatment alternatives considered for the analysis were 4:

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- CAF
  - CAF+CTG
  - CAF+CTG+EMD
  - CAF+ADM with Autogenous Fibroblasts (AF)

52 With 4 treatment options, a total of 6 comparisons were possible.

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54 Three direct comparisons were based on data from RCTs:

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- CAF+CTG vs. CAF+ADM with AF      1 RCT (10 patients)

- CAF+CTG vs. CAF 1 RCT (29 Patients)
- CAF+CTG vs. CAF+CTG+EMD 1 RCT (42 Patients)

Three comparisons were never directly tested in RCTs:

- CAF vs. CAF+ADM with AF
- CAF+CTG+EMD vs. CAF+ADM with AF
- CAF vs. CAF+CTG+EMD

When compared to CAF alone, the greatest mean differences for RES were achieved by the combined CAF+ADM with AF treatment (-1.06, 90%CrI: [-2.23; 0.10]), and then by CAF+CTG (-0.87, 90%CrI: [-1.83; 0.10]). The CAF+ADM with AF combination resulted to be slightly better than CAF+CTG (0.20, 90%CrI: [-0.45; 0.83]), but the estimated difference did not result to be either statistically or clinically significant.

The BNM model produced estimates also on the following treatments: CAF+CTG vs. CAF+CTG+EMD, CAF+ADM with AF vs. CAF+CTG+EMD and CAF vs. CAF+CTG+EMD. However the estimated differences did not result to be either statistically or clinically significant.

All pair-wise comparisons for RES are reported in Table 3.

The *Ranking* of treatments by effectiveness was the following: 1. CAF+ADM with AF (posterior median rank = 1.51); 2. CAF+CTG (1.92); 3. CAF+CTG+EMD (2.97); 4. CAF (3.60) (Table 4, Fig. S1).

The surgical procedures with the highest probability (Pr) of being the *Best* treatments were the combined CAF+ADM with AF treatment (Pr = 64%) and CAF+CTG (Pr = 24%) (Table 4, Fig. S2).

The posterior cumulative ranking probabilities for each treatment in the network are represented in Fig 3. For treatment *i* the Surface under the Cumulative Ranking Curve (SUCRA)

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3 can be interpreted as the average proportion of treatments worse than  $i$ . The largest SUCRA was  
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5 obtained for CAF+ADM (0.83) and for CAF+CTG (0.69).  
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## 8 9 **DISCUSSION**

### 10 11 12 13 *Summary of evidence*

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16 The purpose of the present study was to systematically review the literature on the efficacy of PPS  
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18 procedures to improve esthetics at professional and patient levels. The primary outcomes showed  
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20 that surgical procedures are able to improve aesthetic outcomes at patient level. Secondary  
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22 outcomes demonstrated that PPS is also able to improve esthetics rated by a professional score as  
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24 RES. In the present study a BNM was applied in order to create a network of interventions  
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26 including both direct and indirect comparisons among different trials. The main advantage of using  
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28 a BNM model relies on the opportunity of estimating the *Best* treatment, i.e. the probability that  
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30 each of the root coverage procedures is the best (Lu & Ades 2004,2006) and establishing an  
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32 efficacy *Ranking* among the tested treatments by calculating the posterior distribution of the rank of  
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34 each treatment and its mean.  
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41 The primary aim of the present BNM was to explore the effect of PPS in term of self-perceived  
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43 aesthetic satisfaction. A recent survey (Kim et al. 2014), assessing professional and patient  
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45 satisfaction after root coverage suggested that aesthetic evaluation by periodontist may not always  
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47 be consistent with patient satisfaction. In fact, patient perception seems to be strongly related with  
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49 some RES variables assessing the integration of soft tissue with adjacent tissue while professional  
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51 appraisal seems to be more influenced by the amount of root coverage (Kim et al. 2014). This  
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53 finding suggests that several factors including scar tissue formation and gingival colour may  
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55 influence final patient satisfaction more than the pure root coverage outcomes. Among the possible  
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3 scores to rate patient satisfaction, the visual analogue scale (VAS) obtained increased interest in  
4 recent years to quantify patient outcomes after periodontal therapy (Tonetti et al. 2014). This is a  
5 psychometric response scale used in questionnaires for collecting subjective characteristics that  
6 cannot be directly measured; VAS value is quantified by indicating a position along a continuous  
7 line between two end-points. In the current SR, three RTCs were finally available to perform a NM  
8 on patient aesthetic satisfaction after treatment of single and single plus multiple recessions.  
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10 Interestingly, surgical procedures enclosed in the BNM were associated with a high mean value of  
11 VAS est (85.4) thus suggesting that different techniques may provide high final patient satisfaction.  
12  
13 The surgical procedures with the highest probability of being the *Best* treatments in term of  
14 aesthetics were CAF+CTG treatment (Pr = 44%) and CAF+CTG+EMD (Pr = 26%). This finding  
15 suggests that more effective techniques using CTG in term of clinical efficacy for root coverage  
16 (Cairo et al. 2008; Buti et al. 2011; Buti et al. 2013, Cairo et al. 2014) were also associated with  
17 higher patient satisfaction. On the other hand, it should be kept also in mind that final satisfaction is  
18 not able to capture the possible discomfort after surgery. In fact, the application of CTG requires a  
19 second surgical procedure at the palatal site with longer surgical time, higher post-operative  
20 morbidity and analgesics use (Cortellini et al. 2009; Cairo et al. 2012). Conversely, further studies  
21 evaluating the final aesthetic satisfaction in relation to the specific surgical procedure are mandatory  
22 in order to evaluate possible psychological and socio-economic factors that may influence the  
23 reported outcomes at patient level.  
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47 The second aim of the study was to explore if PPS achieved aesthetic outcomes rated by  
48 professional scores at the operator level. In the modern clinical research the position of the gingival  
49 margin after surgery may be considered restrictive and not be adequate by it self for rating the  
50 overall aesthetic outcome of the treatment. To overcome this limitation, the Root coverage  
51 Aesthetic Score (RES) was introduced. This score is based on the evaluation of five variables: the  
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3 level of the gingival margin, marginal contour, soft tissue surface, position of the MGJ, and gingival  
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5 colour. RES values vary from 0 (final residual recession equal to or higher than the baseline  
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7 recession) to 10 (CRC associated with the fulfilment of the other four variables). A large multi-  
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9 centre study among expert periodontists showed that RES score is a reliable method to assess final  
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11 aesthetics 6 months after periodontal plastic surgery with a total inter-rater agreement of 0.92,  
12  
13 indicating an almost perfect agreement (Cairo et al. 2010). The present BMN showed that PPS  
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15 techniques are associated with high values of RES score after treatment considering the cluster of  
16  
17 studies treating single and single plus multiple recessions; the final mean RES score considering the  
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19 3 studies enclosed in the BNM was 7,9 thus suggesting that different techniques are associated with  
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21 high values of RES score. In the present BMN three combinations of the CAF techniques  
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23 (CAF+CTG, CAF+CTG+EMD, CAF+ADM with AF) were more effective than CAF alone.  
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25 However, the estimated differences were not significant. The surgical procedures with the highest  
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27 probability to be *Best* treatments were the combined CAF+ADM with AF treatment and  
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29 CAF+CTG, thus confirming that grafts improve the effectiveness of CAF alone (Cairo et al. 2008,  
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31 Cairo et al. 2014). Conversely, it should be taken in mind that RES score combined both  
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33 quantitative (amount of root coverage) and qualitative (soft tissue characteristics) variables; the  
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35 current investigation is not able to identify specific interactions between the type of surgical  
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37 procedure and specific aesthetic impairment after treatment (e.g. persistence of scar tissue or  
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39 alteration in colour). Further specific studies investigating associations between patient- and  
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41 surgical-related factors and final aesthetic outcomes are strongly recommended to identify factors  
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43 predicting outcomes after surgery.  
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52 The present BNM showed that all RTCs enclosed in the final analysis are recently published (2001-  
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54 2014) thus suggesting that critical assessment of aesthetic outcomes at both clinical and patient  
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56 level is a very modern approach in clinical research. This temporal trend may be due to the fact that  
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3 changing in paradigms in classical mucogingival surgery started in middle of 90's moving from  
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5 increasing dimension of residual gingiva to the modern periodontal plastic surgery procedure aimed  
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7 at obtaining root coverage and soft tissue aesthetics (Miller 1993, AAP 1996). In addition, current  
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9 patients usually show stringent aesthetic demands and, as consequence, surgical procedures have  
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11 become more sophisticated not only to obtain satisfactory amount of root coverage but also soft  
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13 tissue anatomy comparable to and indistinguishable from adjacent tissue (Cairo et al. 2009). The  
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15 development of specific surgical instruments, sutures and enhancement systems (Burkhardt & Lang  
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17 2005) may represent supporting tools for clinicians to improve final aesthetics of modern  
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19 periodontal plastic surgery.  
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#### 25 *Limitations*

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29 In interpreting the results of the present systematic review, it should be taken into account the  
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31 limited number of trials available for the analysis and the fact that no more than one study included  
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33 in the BNM provided data for the same pair-wise treatment comparison. The lack of information on  
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35 heterogeneity and inconsistency does not imply absence of these sources of variability.  
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#### 40 **CONCLUSIONS**

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42 On the basis of the obtained data and considering the limited evidence available, it appears that:

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47 i) PPS is associated with high patient satisfaction rated by VAS values indicating that CAF+CTG  
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49 with or without the adding of EMD is associated with highest aesthetic satisfaction after healing.  
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52 ii) PPS improve soft tissue aesthetics rated by means Root Coverage Aesthetics Score; in particular  
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54 grafting CAF is associated with higher values of RES score than CAF alone.  
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**Indications for future research**

i) Increased number of RCTs evaluating the patient satisfaction after root coverage procedures is suggested

ii) The potential effect of patient satisfaction and preference should be evaluated in further studies dealing on periodontal plastic surgery

iii) Increased number of RCTs evaluating the aesthetic outcomes of root coverage procedures using professional methods is suggested

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**Table Captions:**

**Table 1:** RCTs presenting evaluation of aesthetic outcomes included in the SR

**Table 2:** Studies included in the Network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single and multiple recessions.

**Table 3:** Results of the Bayesian network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single plus multiple recessions.

**Table 4:** *Ranking* in efficacy and *Best* for RES and VAS Est outcomes for single recessions.

**Figures Legends:**

**Figure 1:** PRISMA flow chart

**Figure 2:** Network plot for RES (a) and VAS Est (b) showing: direct pair-wise comparisons (continuous lines); both direct and indirect pair-wise comparisons (dotted lines); risk of bias estimation (green color = low risk; yellow = moderate risk; and red = high risk of bias). Nodes are weighted according to the number of studies including the respective intervention. Edges are weighted according to the number of studies including the respective comparison.

**Figure 3:** Cumulative ranking curves and surfaces under these curves (SUCRA) for RES and VAS Est.

**SUPPORTING INFORMATION****Supporting Figures**

**Figure S1:** Ranking Graph for VAS Est. Treatments with the higher ranking are positioned on the left side of the graph: as lower the values of the ranking as higher the position of the treatment in the grading of efficacy (i.e.: CAF+CTG is the treatment with the highest ranking). The bubble size

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3 is directly proportional to the probability that the treatment is the *Best*: as greater the bubble as  
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5 higher the *Best*  
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7 **Figure S2:** Ranking Graph for RES. : Treatments with the higher ranking are positioned on the left  
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9 side of the graph: as lower the values of the ranking as higher the position of the treatment in the  
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11 grading of efficacy (i.e.: CAF+ADM with AF is the treatment with the highest ranking). The bubble  
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13 size is directly proportional to the probability that the treatment is the *Best*: as greater the bubble as  
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15 higher the *Best* (i.e.: CAF+ADM with AF is the treatment with the highest *Best*).  
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## 20 **Supporting Experimental Procedures**

21 **Methods S1:** Study selection

22 **Methods S2:** Information sources and Search

23 **Methods S3:** Data collection process

24 **Methods S4:** Risk of bias in individual studies

25 **Methods S5:** Bayesian network meta-analysis  
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## 36 **Supporting Data**

37 **Data S1:** Rejected studies.

38 **Data S2:** Study characteristics and Risk of bias within studies  
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## 45 **Supporting Information**

46 **Appendix S1:** References excluded studies  
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Table 1. RCTs presenting evaluation of aesthetic outcomes included in the SR

Study	Comparison/ Type of defect	Study Design	MRC Test (%)	MRC Control (%)	CRC test (%)	CRC control (%)	Professional aesthetic evaluation/outcomes	Patient aesthetic evaluation/outcomes
Aichelmann-Reidy et al. (2001)	CAF+ADM <i>versus</i> CAF+CTG/single recession	SM	65.9	74.1	31.8	50.0	quality assessment as excellent, good, fair and poor for different parameters (colour match, contour, contiguity, lack of keloid formation)/ Raw data presented with no statistical analysis (e.g. excellent colour match in 18 cases in the test group and 7 in the control group)	Quality assessment as excellent, good, fair and poor/13 versus 8 excellent (no statistical analysis)
Wang et al. (2001)□	CAF+GTR <i>versus</i> CAF+CTG/single recession	SM	73	84	43.7	43.7	quality assessment of colour match, contour, consistency, contiguity and keloid formation/ Raw data presented with no statistical analysis (e.g. excellent colour match in 16 cases in the test group and 14 in the control group)	Evaluation of colour match, overall satisfaction and amount of root coverage as excellent, good, and fair / Higher satisfaction reported for the control group (no statistical analysis)
McGuire & Nunn 2003	CAF+EMD <i>versus</i> CAF+CTG/single recession	SM	95.1	93.8	89.5	79.0	Colour, texture and contour/ No difference for colour and texture, while significant difference for contour favoring test (8 sites versus 1) (data reported in the 10 year follow-up by McGuire et al. 2012)	Patient preference between test and control site/ no significant difference (reported at 10 year follow-up by McGuire et al. 2012)
Mahajan et al. (2007)	CAF+ADM <i>versus</i> CAF/single recession	P	97.1	77.4	NR	NR	NR	Patient rated satisfaction with points 1 to 3 of several parameters including colour of gums and shape and contour of gums/ 18.4 versus 19, no significant difference
McGuire & Scheyer (2010)	CAF+CM <i>versus</i> CAF+CTG/single recession	SM	88.5	99.3	NR	NR	Color and texture binary rated as "equal or not equal to surrounding native tissue" through visual observation/ no difference reported (data not shown)	Patients satisfaction evaluated as "unsatisfied" or "satisfied" or "very satisfied" level/ no difference reported (data not shown)
Jhaveri et al. (2010)	CAF+ADM+Fib <i>versus</i> CAF+CTG/single recession	SM	83.3	83.3	70.0	60.0	Root coverage Aesthetic Score (RES)/ 8.1 versus 7.9, no significant difference	NR
Cairo et al. 2012	CAF+CTG <i>versus</i> CAF/ single recession	P	85.0	69.0	57.0	29.0	Root coverage Aesthetic Score (RES)/ 7.6 versus 6.7 (no difference)	Visual analogue scale (VAS) (0-100)/ 80.4 versus 75.0 (no difference)

Zucchelli et al. 2012	LPF <i>versus</i> CAF + CTG / only single recessions at molars	P	74.2	88.8	4	48	Visual analogue scale (VAS) (0-100) / 91.2 <i>versus</i> 89.6 (No difference)	Visual analogue scale (VAS) (0-100) for colour match/ 92.3 <i>versus</i> 95.6 (No difference)  Number of cases with "Keloid" formation/ 6 <i>versus</i> 3 (no difference)
Aroca et al. 2013	MCAT+ CM <i>versus</i> MCAT + CTG / multiple recessions	SM	71	90	22	50	NR	Visual analogue scale (VAS) (0-100)/ 90.6 <i>versus</i> 92.6* (No difference)
Roman et al. 2013	CAF+CTG+EMD <i>versus</i> CAF+CTG/ single and multiple recessions	P	82.2	89.7	56.5	70.6	Root coverage Aesthetic Score (RES)/ 8.6 <i>versus</i> 9.0 (no difference)	Visual analogue scale (VAS) (0-10)/ 8.7 <i>versus</i> 8.9 (no difference)
Ahmedbeyli et al. 2014	CAF+ADM <i>versus</i> CAF/ multiple recessions	P	94	74	83	50	Root coverage Aesthetic Score (RES)/ 9.08 <i>versus</i> 7.58 (favouring test)	Patient satisfaction score/ 18.83 <i>versus</i> 17.33 (no difference)
Salhi et al. JCP 2014	Pouch+CTG <i>versus</i> CAF+CTG/ single recession	P	91.3	96.3	79	89.5	Pink Aesthetic Score/ 11.6 <i>versus</i> 11 (No difference reported)	A 0-10 scale/ no difference reported (data not shown)
Zucchelli et al. 2014	CAF+CTG <i>versus</i> CAF/ multiple recessions	P	97	90	91	78	Visual analogue scale (VAS) (0-100)/ 81.6 <i>versus</i> 82.8 (no difference)	Visual analogue scale (VAS) (0-100) to assess color match and counter/ For color match: 73.6 <i>versus</i> 85.2 (favouring control) For counter: 87.2 <i>versus</i> 76.8 (favouring test)
Zuhr et al. 2014	TT+CTG <i>versus</i> CAF+EMD/single and multiple recessions	P, some patient treated with SM design	98.4	71.8	80	15.4	Root coverage Aesthetic Score (RES)/ 9.08 <i>versus</i> 6.92 (favouring test)	Visual analogue scale (VAS) (0-10)/ 9.21 <i>versus</i> 9.07 (no difference)
Milinkovic et al. 2015	Fib +CAF <i>versus</i> CAF+CTG /single and multiple recessions	SM	89.9%	91.3%	NR	NR	Root coverage Aesthetic Score (RES)/ 8.67±1.41 <i>versus</i> 8.61±1.28 (no difference)	NR
Ozenci et al. 2015	TT+ADM <i>versus</i> CAF+ADM	P	75.7%	93.8%	37.4	85%	Root coverage Aesthetic Score (RES)/ 7.30 ±1.25 <i>versus</i> 8.90± 1.60 (favouring control group)	Patient satisfaction score/ 17.10 ± 1.66 <i>versus</i> 18.50 ± 1.71(favouring control group)

### Legend

**SM:** Split Mouth design; **P:** Parallel design; **MRC:** Mean % of Root Coverage; **CRC:** Complete Root Coverage; **NR:** Not Reported; **CAF:** Coronally Advanced Flap; **CTG:** subepithelial Connective Tissue Graft ; **GTR:** Guided Tissue Regeneration procedures for root coverage; **EMD:** Enamel Matrix Derivative; **ADM:** Acellular Dermal Matrix; **CM:** porcine Collagen Matrix; **LPF:** Laterally Positioned Flap; **β-TCP:** Beta-Tricalcium Phosphate; **rhPDGF-BB:** Recombinant Human Platelet-Derived Growth Factor-BB; **Fib:** autologous gingival Fibroblasts; **MCAT:** Modified Coronally Advanced Tunnel; **Pouch:** Pouch Technique; **TT:** Tunnel Technique

\*data provided by contact author



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Table 2. Studies included in the Network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single and multiple recessions.

STUDY	TR. COMPARISON	RES Mean diff. (SD)	VAS Est Mean diff. (SD)	F-UP	STUDY DESIGN
Jhaveri et al. (2010)	CAF+CTG vs. CAF+ ADM with autologous fibroblasts (AF)	0.20 (0.39)	-	6	RCT, split mouth design
Cairo et al. (2012)	CAF+CTG vs. CAF	-0.86 (0.59)	-5.36 (5.58)	6	RCT, parallel study design
Roman et al. (2013)	CAF+CTG vs. CAF+CTG+EMD	-0.42 (0.41)	-2.50 (4.72)	12	RCT, parallel study design
Zucchelli et al. (2012)	CAF+CTG vs. LPF	-	-1.60 (2.44)	12	RCT, parallel study design

A positive value of "RES" or "VAS Est" is to be interpreted as a difference in efficacy in favor of the second treatment when compared to the first, as shown in the column "Tr. Comparison" (i.e. in the CAF+CTG vs. CAF+ADM with AF comparison for RES, CAF+ADM with AF shows a mean difference of 0.20 mm greater than CAF+CTG).

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Table 3. Results of the Bayesian network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single plus multiple recessions.

Tr. Comparison	Type of Comparison	RES		VAS Est	
		Est.	90% CrI	Est.	90% CrI
CAF+CTG vs. CAF+ADM with AF	DC	0.20	-0.45; 0.83	-	-
CAF+CTG vs. CAF	DC	-0.87	-1.83; 0.10	-5.42	-14.56; 3.73
CAF+CTG vs. CAF+CTG+EMD	DC	-0.42	-1.10; 0.26	-2.49	-10.31; 5.29
CAF+ADM with AF vs. CAF	IC	-1.06	-2.23; 0.10	-	-
CAF+ADM with AF vs. CAF+CTG+EMD	IC	-0.62	-1.55; 0.32	-	-
CAF vs. CAF+CTG+EMD	IC	0.45	-0.73; 1.62	2.93	-9.08; 14.86
CAF+CTG vs. LPF	DC	-	-	-1.63	-5.65; 2.35
LPF vs. CAF	IC	-	-	-3.79	-13.78; 6.16
LPF vs. CAF+CTG+EMD	IC	-	-	-0.86	-9.63; 7.84

“Est.” is the mean of the posterior distribution under NM model. A positive value of “Est.” is to be interpreted as a difference in efficacy in favor of the second treatment when compared to the first, as shown in the column “Tr. Comparison” (i.e. in the CAF+CTG vs. CAF+ADM with AF comparison in the NM model for RES, CAF+ADM with AF shows a mean difference of 0.20 mm greater than CAF+CTG). DC = Direct Comparison; IC = Indirect Comparison.

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Table 4. *Ranking* in efficacy and *Best* for RES and VAS Est outcomes for single recessions.

Treatment	RES		VAS Est	
	Ranking	Best	Ranking	Best
	Est.	Pr.	Est.	Pr.
CAF	3.60	0.04	3.23	0.13
CAF+CTG	1.92	0.24	1.71	0.44
CAF+CTG+EMD	2.97	0.08	2.61	0.26
CAF+ADM with autologous fibroblasts	1.51	0.64	-	-
LPF	-	-	2.45	0.18

“Est.” is the mean of the posterior distribution under the NM model; as lower the values of the ranking as higher the position of the treatment in the grading of efficacy; “Pr.” is the probability that each treatment is the *Best*.

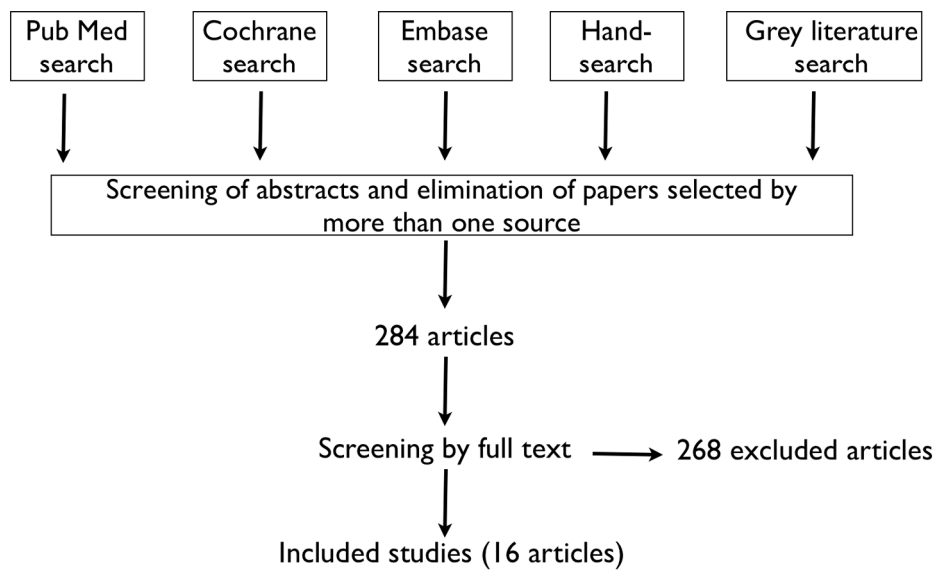


Figure 1: PRISMA flow chart.  
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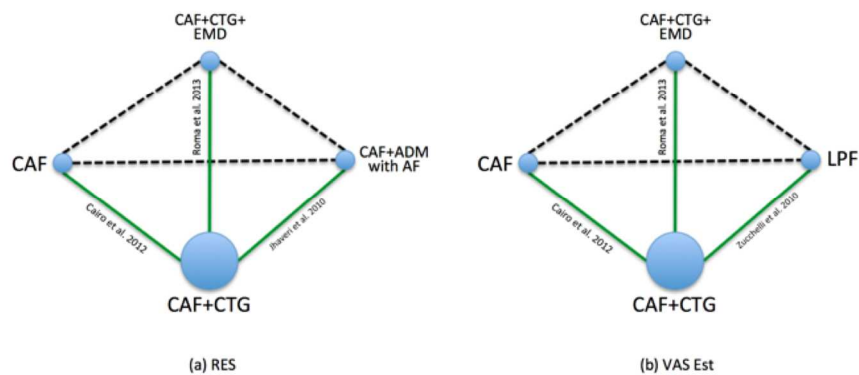


Figure 2: Network plot for RES (a) and VAS Est (b) showing: direct pair-wise comparisons (continuous lines); both direct and indirect pair-wise comparisons (dotted lines); risk of bias estimation (green color = low risk; yellow = moderate risk; and red = high risk of bias). Nodes are weighted according to the number of studies including the respective intervention. Edges are weighted according to the number of studies including the respective comparison.

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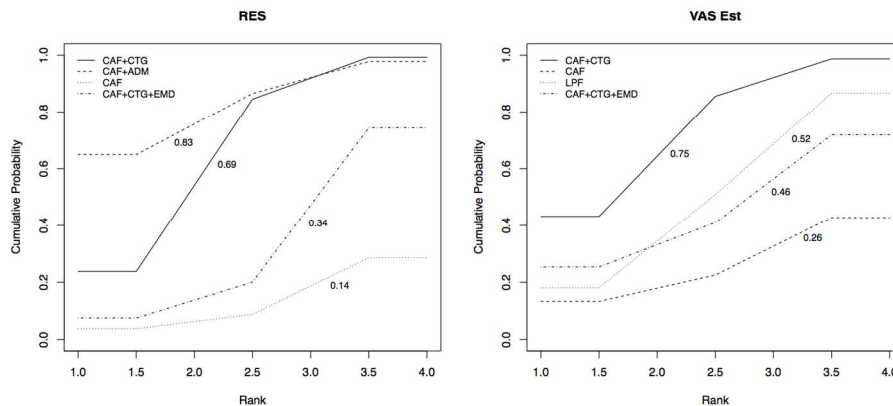


Figure 3: Cumulative ranking curves and surfaces under these curves (SUCRA) for RES and VAS Est.  
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## Methods S1-Study selection

In order to produce valid results and to hold the assumption of transitivity, the distribution of potential effect modifiers judged as relevant for the combination of quantitative data analyses was estimated and resulted balanced. In particular, criteria for study selection took into account:

- A) Similar population characteristics: average patient age and gender distribution
- B) Consistent outcome measures: well-defined patient evaluation and/or a standardized clinical assessment.

Studies regarding single and multiple gingival recessions were evaluated separately. When RCTs covering the treatment of both single and multiple recessions were retrieved, these were considered in the group of single recession treatment since the used surgical procedure was originally designed for single defects but extended also to multiple recessions.

## Methods S2-Information sources and Search

For the identification of the studies investigated in this review and published until April 2013, the register of clinical studies published in previous systematic reviews (Cairo et al. 2014, Graziani et al. 2014) was consulted. For the identification of RTCs published from May 2013 to January 2016, an electronic search was performed using three on-line evidence sources by expert operators (UP and FC):

1. The National Library of Medicine (*MEDLINE* by PubMed), using the strategy: (“Gingival Recession/surgery” [Mesh] OR “Gingival Recession/ therapy” [Mesh]) AND ((Humans [Mesh]) AND (Randomized Controlled Trial[ptyp]));
2. The *Cochrane Oral Health Group Trials Register*, using the following strategy: “Gingival Recession” [Search All Text] AND “Root Coverage” [Search All Text];
3. EMBASE, utilizing the strategy: “Gingival Recession”[Mesh] AND (Randomized Controlled Trial).

Hand searching was also performed by 3 independent reviewers (FC, FG and UP) on the following journals: *Journal of Clinical Periodontology*, *Journal of Periodontology*, *Journal of Periodontal Research*, *International Journal Periodontics and Restorative Dentistry*. Early view/accepted articles sections were also consulted at corresponding web site.

By merging items provided by electronic search with articles retrieved with the hand search, a final collecting file with all potentially included RCT was created.

### Methods S3-Data collection process

Eligibility assessment was performed through titles/abstract analysis and full-text analysis. Titles and abstracts of the search results were initially screened by the three reviewers (UP, FG and FC), for possible inclusion in the review. To avoid excluding potentially relevant articles, abstracts providing an unclear result were included in the full-text analysis. The full-text of all studies of possible relevance was then obtained for independent assessment by reviewers against the stated inclusion criteria. Disagreement was solved through discussion. The reviewers conducted all quality assessments independently. In case of controversial data interpretation, authors of the enclosed studies were contacted by e-mail.

### Methods S4-Risk of bias in individual studies

The quality assessment of the included trials was independently performed by reviewers according to the Cochrane Handbook Systematic Review of Interventions (2011). Six main quality criteria were examined: sequence generation, allocation concealment, blinding of participants, personal and outcomes assessors, incomplete data outcomes, selective outcome reporting, and other possible source of bias.

After quality assessment, studies were grouped into 2 categories:

- A) Low risk of bias, if all 6-quality criteria were met.
- B) High risk of bias, if one or more of the quality criteria was not met.

## Methods S5. Bayesian network meta-analysis

The proposed model is a simplified version of the one proposed by Lu&Ades (2004,2006) for networks of two-arm trials (Buti 2011). It is a fixed-effects model, which assumes consistency among direct and indirect comparisons:

$$Y_{jkk} \sim N(d_{bk}, \sigma_{jkk}^2)$$

where:

$j = \text{study};$

$k, b = \text{treatments};$

$Y_{jkk} = \text{estimate of the effect of treatment } k \text{ when compared with } b \text{ in the } j\text{th trial};$

$\sigma_{jkk} = \text{estimated standard error of } Y_{jkk}.$

$d_{bk} = \text{average effect of treatment } k \text{ when compared with } b.$

The relative treatment effects  $d_{bk}$  were expressed in terms of mean differences for the continuous outcomes variable. The only source of variability is that within study.

Non-informative vague priors were specified for the effect measures  $d_{bk}$  ( $N(0, 10^6)$ ).

### *Ranking and Best*

The advantage of using a Bayesian approach relies on the following issues:

- estimating the *Best* treatment, i.e. the probability that each of the root coverage procedures is the best (Lu & Ades 2004,2006);
- establishing an efficacy *Ranking* among the tested treatments by calculating the posterior distribution of the rank of each treatment and its mean.

For both outcomes, the posterior cumulative ranking curves were plotted for each treatment and the area under these curves (SUCRA) was calculated (Salanti et al. 2011).

### *Network heterogeneity and inconsistency*

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3 The present BNM model was based on the assumption of lack of the two main  
4 sources of variability that can be usually detected in NM models: the between-trials  
5 heterogeneity (Higgins & Thompson 2002, Edwards et al. 2009) and the network  
6 inconsistency. This assumption was considered adequate because of the very few  
7 evidence available from trials for the analysis. In fact, no more than one study  
8 included in the BNM provided data for the same pair-wise treatment comparison; and  
9 no one of the presented comparisons was supported by both direct and indirect  
10 evidence. It should be stressed that this model assumption does not imply the absence  
11 of heterogeneity and inconsistency in the NM, but only express lack of information on  
12 these two variance components.  
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#### 20 21 *Estimation method and software*

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23 A Markov Chain Monte Carlo approach was used to obtain a sample from the  
24 joint posterior distribution of the parameters for NM models. Three chains of 100,000  
25 iterations were generated, and then one sample out of the five was used after a  
26 50,000-run burn-in. The convergence of the chains was checked by the method of  
27 Gelman & Rubin (1992). The marginal distributions of the parameters of interest were  
28 summarized by the posterior mean, the median and the 90% credibility interval, i.e.  
29 the 5th and 95th percentiles of the simulated values (Sterne et al 2001). All the  
30 analyses were performed using WinBUGS software, version 1.4.3 (Spiegelhalter et al.  
31 2003) and R software (Comprehensive R Archive Network - [http://CRAN.R-  
32 Project.org](http://CRAN.R-Project.org)).  
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Data S1- Rejected studies

RCTs reporting aesthetic outcomes not included in the systematic review and related reason

Reason for exclusion	RCT
Study on heavy smokers	Alves et al. 2012
Variation of the same surgical procedure	Bouchard et al.1994; Zucchelli et al 2003; Francetti et al. 2005; Zucchelli et al. 2009; Zucchelli et al. 2010; Ozcelik et al. 2011; Bittencourt et al. 2012; Zucchelli et al. 2014b; Zucchelli et al. 2014c; Fernandes-Dias et al. 2015;

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### Data S2-Study characteristics and Risk of bias within studies

Among the total 16 RTCs selected in the SR (Table 1), 9 studies were focused on the treatment of the single gingival recession (Aichelmann-Reidy et al. 2001; Wang et al. 2001; McGuire & Nunn 2003; Mahajan et al. 2007; McGuire & Scheyer 2010; Jhaveri et al. 2010; Cairo et al. 2012; Zucchelli et al. 2012; Salhi et al. 2014), 2 RCTs enclosed both single and multiple recessions (Roman et al. 2013; Zuhr et al. 2014; Milinkovic et al. 2015), while the remaining 5 were focused on the treatment of multiple recessions (Aroca et al. 2013; Zucchelli et al. 2014; Ahmedbeyli et al. 2014; Ozenci et al. 2015).

Among the possible approaches to rate patient satisfaction, the Visual Analogue Scale (VAS) was applied in 7 RCTs (57%) (Cairo et al. 2012; Zucchelli et al. 2012; Aroca et al. 2013; Roman et al. 2013; Zucchelli et al. 2014; Salhi et al. 2014; Zuhr et al. 2014). Heterogeneous scoring systems were applied in 6 RCTs (Aichelmann-Reidy et al. 2001; Wang et al. 2001; Mahajan et al. 2007; McGuire & Scheyer 2010; Ahmedbeyli et al. 2014; Ozenci et al. 2015). In two studies patient satisfaction was not rated (Jhaveri et al. 2010; Milinkovic et al. 2015) while patient preference was assessed in the 10-year follow-up (McGuire et al. 2012) of McGuire & Nunn 2003.

Among the possible professional approaches to rate aesthetic outcomes, the Root coverage Aesthetic Score (RES) was applied in 7 RCTs (43%) (Jhaveri et al. 2010; Cairo et al. 2012; Roman et al. 2013; Zuhr et al. 2014; Ahmedbeyli et al. 2014; Ozenci et al. 2015; Milinkovic et al. 2015). Other approaches included heterogeneous scoring systems (Aichelmann-Reidy et al. 2001; Wang et al. 2001; McGuire & Scheyer 2010), the Visual Analogue Scale (VAS) for operators (Zucchelli et al. 2012; Zucchelli et al. 2014), the assessment of some qualitative parameters (McGuire & Nunn 2003) and the Pink Aesthetic Score (Salhi et al. 2014). In 2 RCTs enclosed in the SR (Mahajan et al. 2007; Aroca et al. 2013) no professional evaluation of the aesthetic outcomes was performed.

Randomization was reported in all studies included in the present systematic review. After quality assessment, 4 RCTs were classified as studies at a low risk of bias (McGuire et al. 2010, Cairo et al. 2012, Zucchelli et al. 2012 and Zucchelli et al. 2014).



## Appendix S1-references excluded studies

Alves, L.B., Costa, P.P., Scombatti de Souza, S.L., de Moraes Grisi, M.F., Palioto, D.B., Taba Jr, M., Novaes Jr, A.B. Jr. (2012) Acellular dermal matrix graft with or without enamel matrix derivative for root coverage in smokers: a randomized clinical study. *Journal of Clinical Periodontology* **39**(4):393-9. doi: 10.1111/j.1600-051X.2012.01851.x

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3 *Periodontology* 37(8):728-38. doi: 10.1111/j.1600-051X.2010.01550.x.  
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6 Zucchelli, G., Marzadori, M., Mounssif, I., Mazzotti, C., Stefanini, M. (2014). Coronally advanced  
7 flap + connective tissue graft techniques for the treatment of deep gingival recession in the lower  
8 incisors. A controlled randomized clinical trial. *Journal of Clinical Periodontology* 41(8):806-13.  
9 doi: 10.1111/jcpe.12269.  
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12 (2014). Does the dimension of the graft influence patient morbidity and root coverage outcomes? A  
13 randomized controlled clinical trial. *Journal of Clinical Periodontology* 41(7):708-16. doi:  
14 10.1111/jcpe.12256.  
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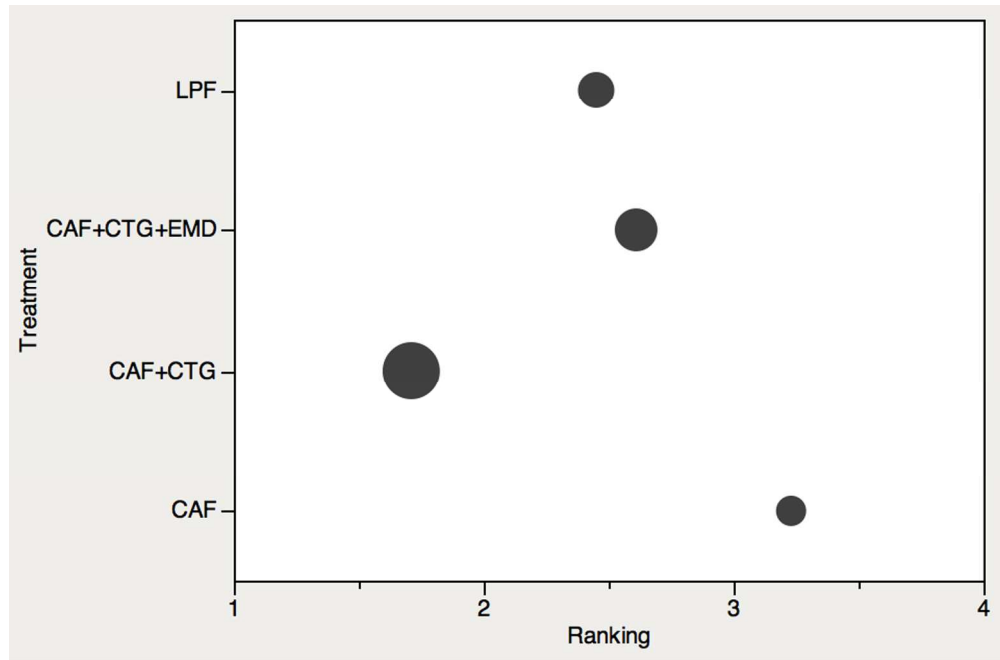


Figure S1: Ranking Graph for VAS Est. Treatments with the higher ranking are positioned on the left side of the graph: as lower the values of the ranking as higher the position of the treatment in the grading of efficacy (i.e.: CAF+CTG is the treatment with the highest ranking). The bubble size is directly proportional to the probability that the treatment is the Best: as greater the bubble as higher the Best

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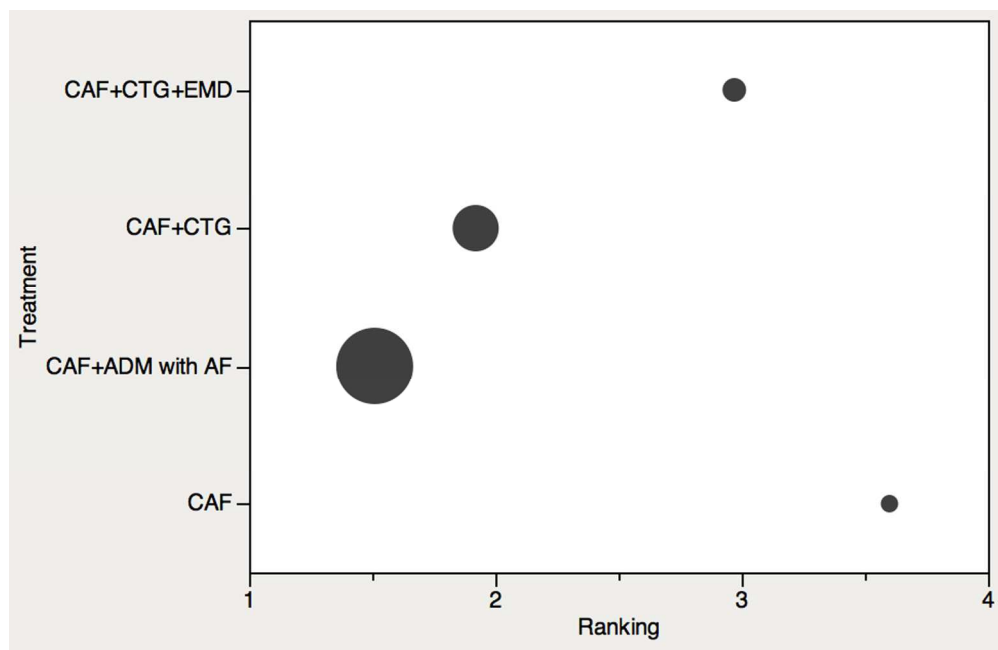


Figure S2: Ranking Graph for RES. : Treatments with the higher ranking are positioned on the left side of the graph: as lower the values of the ranking as higher the position of the treatment in the grading of efficacy (i.e.: CAF+ADM with AF is the treatment with the highest ranking). The bubble size is directly proportional to the probability that the treatment is the Best: as greater the bubble as higher the Best (i.e.: CAF+ADM with AF is the treatment with the highest Best).  
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4 Dear Editor

5 All suggestions by referees were carefully considered and used to improve the manuscript.  
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7 In the revised paper the systematic review was updated until January 2016. Furthermore, the  
8 concept of network meta-analysis was explained in the introduction section. Please note that  
9 some paragraphs were moved into the additional material section.  
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14 We hope that the manuscript meets the expectancies of the journal in this form  
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18 Best regards

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20 Francesco Cairo  
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23 Specific Comments  
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26 Associate Editor ☐Comments to the Author: ☐In light of the comments by one of the reviewers  
27 the authors should improve the introduction with better explanation of the concept of  
28 network meta-analysis and secondly they should update their review with publications in the  
29 last 12 months. A revised paper including these recommendations should be sent.  
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34 Reply: According to referee indications, the introduction was modified as suggested  
35 explaining the concept of network meta-analysis. In addition, the systematic review was  
36 updated until January 2016, thus increasing literature search of 12 months as suggested.  
37 Please note also that some paragraphs were moved into the additional material section.  
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48 Referee: 1 ☐☐Comments to the Author ☐I appreciate the efforts of the authors in  
49 incorporating most of my previous suggestions, as well as in providing explanations to my  
50 previous comments. The current version of their systematic review will certainly provide new  
51 insights to the importance of patient-reported outcomes. I am very satisfied with the  
52 manuscript and consider it ready for publication in the Journal of Clinical Periodontology. ☐☐  
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59 Reply: thank you for your comment  
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5 Referee: 2 ☐☐Comments to the Author

6 ☐Dear Authors, ☐The manuscript has clearly been improved in this new version. There are  
7 however some comments that needs to be addressed: ☐☐

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9  
10 1. Abstract ☐M&M: please start this section with the description of the systematic review  
11 rather than with data analyses section. ☐☐

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13 Reply: The section was modified as suggested

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16 2. Scientific rationale ☐Please change to assess the efficacy to “to compare the efficacy” ☐☐

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18 Reply: the paragraph was modified as suggested

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21 3. Introduction ☐Page 49. Lines 11-17: Please add a more specific information regarding  
22 Network meta-analyses. It is not correct that it does not summarize direct comparison. I could  
23 be a good idea to explain the readers of the concept of direct and indirect comparisons in  
24 order to better understand the meaning of a network MA. ☐In addition, the concept of  
25 transitivity and its importance in NMA should be added in the introduction. If not, it seems  
26 that NMA is going to solve the problems of MA when few and heterogeneous articles are  
27 found, and that it is not the case.

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35 Reply: the introduction was modified as suggested. The following paragraph was added:  
36 Network meta-analysis (also called the Mixed-Treatment Comparisons) (Lumley 2002) was  
37 developed as a new approach to meta-analysis. Different from standard meta-analytical  
38 techniques, allowing single separate pair-wise, head-to-head, comparisons, NM is able to  
39 combine evidence from both direct and indirect comparisons from different trials in a unique  
40 network of treatments (Buti et al. 2011). In presence of several treatments for the same  
41 condition, lack of all possible comparisons is frequently recognised in the body of literature  
42 and only indirect inference is possible on the comparisons that are not informed by data.  
43 However, the use of indirect comparison methods and the results of the analysis must be  
44 interpreted with caution. When planning a NM, it is important to assess patient and study  
45 characteristics across the studies that compare pairs of treatments to understand if the  
46 distribution of effect modifiers such as age, gender, disease severity, consistency of  
47 treatments in intervention trials is similar across studies (Hutton et al. 2015).  
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5 4. Material and methods This systematic review is performed until January 2015,  
6 however we are in April 2016. I would suggest the authors to update it.  
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10 Reply: according to your suggestion, the systematic review was updated until January 2016.  
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13 Risk of bias assessment: There is a newer version of the Cochrane Handbook (2011). Please  
14 update  
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18 Reply: Bias assessment was performed according to Cochrane Handbook 2011 as suggested.  
19 Please note also that some paragraphs were moved into the additional material section.  
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# Root Coverage procedures improve patient aesthetics. A Systematic Review and Bayesian network meta-analysis.

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**Source of Funding:** The study was self founded by authors.

**Key words:** gingival recession, aesthetics, systematic review, meta-analysis.

**Running title:** Aesthetics after root coverage.



## ABSTRACT

**Background:** The aim of this study was to perform a systematic review (SR) of randomized controlled trials (RCTs) to explore if periodontal plastic surgery procedures for the treatment of single and multiple gingival recessions (Rec) may improve aesthetics at patient and professional levels.

**Material and Methods:** In order to combine evidence from direct and indirect comparisons by different trials a Bayesian network meta-analysis (BNM) was planned. A literature search on PubMed, Cochrane libraries, EMBASE, and hand-searched journals until January 2015 was conducted to identify RCTs presenting aesthetic outcomes after root coverage using standardized evaluations at patient and professional level.

**Results:** A total of 16 RCTs were selected in the SR; 3 RCTs presenting professional aesthetic evaluation with Root coverage Aesthetic Score (RES) and 3 showing final self-perception using the Visual Analogue Scale (VAS Est) could be included in a BNM model. Coronally Advanced Flap plus Connective Tissue Graft (CAF+CTG) and CAF+Acellular Dermal Matrix (ADM) and Autologous Fibroblasts (AF) were associated with the best RES outcomes (best probability = 24% and 64%, respectively), while CAF+CTG and CAF+CTG+Enamel matrix Derivatives (EMD) obtained highest values of VAS Est score (best probability = 44% and 26%, respectively).

**Conclusions:** Periodontal Plastic Surgery (PPS) techniques applying grafts underneath CAF with or without the adding of EMD are associated with improved aesthetics assessed by final patient perception and RES as professional evaluation system.

## CLINICAL RELEVANCE

### *Scientific rationale for the study:*

To compare, using a Bayesian network meta-analysis, the efficacy of periodontal plastic surgery procedures to improve aesthetics as assessed by professional and patient scores.

### *Principal findings:*

Coronally Advanced Flap plus Connective Tissue Graft (CAF+CTG) and CAF plus Acellular Dermal Matrix (ADM) and Autologous Fibroblasts (AF) were associated with the highest professional outcomes rated by means of Root Coverage Aesthetics Score (RES). CAF+CTG and CAF+CTG plus Enamel Matrix Derivatives (EMD) obtained highest values in term of patient satisfaction rated by Visual Analogue Scale (VAS est).

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3 *Practical implications:*

4 Grafting underneath the Coronally Advanced Flap with or without the adding of Enamel Matrix  
5 Derivatives is associated with highest aesthetic outcomes at professional and patient level.  
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For Peer Review

## INTRODUCTION

Aesthetic concern is a primary indication for treatment of gingival recession (AAP 1996). In the last decade a large amount of data have shown that different procedures are effective in obtaining root coverage. Randomized clinical trials (RCTs) and systematic reviews (SRs) showed that combination of coronally advanced flap and connective tissue graft (CAF+CTG) is associated with the highest probability to achieve complete root coverage for single gingival recession with no loss of interproximal attachment (Cairo et al. 2008; Chambrone et al. 2008, 2010, Cortellini et al. 2009; Cairo et al. 2014, Pini Prato et al. 2014, Chambrone & Tatakis 2015). Emerging data also showed similar clinical outcomes at single gingival recession with loss of interproximal attachment (Cairo et al. 2012; Cairo et al. 2015). Furthermore, the efficacy of surgical procedures in cases of multiple gingival recessions is less investigated (Graziani et al. 2014). On the other hand, a recent SR regarding untreated recession defects in subjects with good oral hygiene shows high probability of progressing during long-term follow-up (Chambrone & Tatakis 2016)

Although several papers on root coverage usually described aesthetic request as the reason for treatment, clinical outcomes are generally reported only in terms of the percentage of root coverage and number of sites with complete root coverage (CRC). Unfortunately, the sole evaluation of the level of the gingival margin position following surgery may be not adequate to assess final soft tissue quality.

Recently, some methods to evaluate aesthetic outcomes after root coverage have been suggested in order to standardize the qualitative assessment of healed soft tissue over root surface (Kerner et al. 2009, Cairo et al. 2009). In addition, the collection of patient-related outcomes including aesthetics satisfaction has been recommended for clinical trials on root coverage procedures (Rocuzzo et al. 2002; Chambrone et al. 2010, Tonetti et al. 2014).

Previous systematic reviews in periodontal plastic surgery (Cairo et al. 2008, Cairo et al. 2014) failed to perform meta-analysis by means of conventional systems concerning aesthetic outcomes due to the presence of few and heterogeneous data among studies. Network meta-analysis (also called the Mixed-Treatment Comparisons) (Lumley 2002) was developed as a new approach to meta-analysis. Different from standard meta-analytical techniques, allowing single separate pair-wise, head-to-head, comparisons, NM is able to combine evidence from both direct and indirect

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3 comparisons from different trials in a unique network of treatments (Buti et al. 2011). In presence  
4 of several treatments for the same condition, lack of all possible comparisons is frequently  
5 recognised in the body of literature and only indirect inference is possible on the comparisons that  
6 are not informed by data. However, the use of indirect comparison methods and the results of the  
7 analysis must be interpreted with caution. When planning a NM, it is important to assess patient and  
8 study characteristics among studies that compare pairs of treatments to understand if distribution of  
9 effect modifiers such as age, gender, disease severity, consistency of treatments in intervention  
10 trials is similar across studies (Hutton et al. 2015).  
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18 The purpose of this study was to conduct a systematic review of RCTs to explore if root coverage  
19 procedures are effective to improve aesthetics assessed by professional evaluation system and final  
20 patient perception. A Bayesian Network Meta-analysis (BNM) model has been considered in order  
21 to summarize quantitative data from included RCTs.  
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## MATERIAL AND METHODS

### Protocol development and Eligibility criteria

A detailed protocol was reported according to the PRISMA (Preferred Reporting Items Systematic review and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions (Liberati et al. 2009; Moher et al. 2009; Hutton et al. 2015) (Fig 1). The focused question of this systematic review was “*Is periodontal plastic surgery for root coverage effective to improve aesthetics at patient and/or operator level?*” Only RCTs in English language in the field of periodontal plastic surgery and evaluating aesthetic outcomes with standardized procedures were included.

### Study selection

The criteria for considering studies for this review were organized by the PICO method (Glossary of Evidence-Based Terms 2007) and were as follows:

(P) Type of participants: patients with a clinical diagnosis of localized or multiple gingival recessions. Studies involving only heavy smokers ( $\geq 10$  cigarettes/day) were not enclosed in the SR.

(I) Type of interventions: any type of surgical treatment including possible combinations for treatment of localized or multiple gingival recession defects.

(C) Comparison between interventions: any type of possible comparison between surgical treatments for root coverage, excluding variations of the same technique, with at least 6 months of follow-up.

(O) Type of outcome measures:

Primary outcome was aesthetic assessment of root coverage outcomes using a well-defined patient evaluation and/or a standardized clinical assessment. Aesthetic evaluations using empiric or unclear approaches were not considered.

Studies regarding single and multiple gingival recessions were evaluated separately. When RCTs covering the treatment of both single and multiple recessions were retrieved, these were considered in the group of single recession treatment since the used surgical procedure was originally designed for single defects but extended also to multiple recessions. Further information is presented in appendix 1.

### Information sources and Search

RTCs dealing on root coverage procedures were selected up to January 2016. Details of search were presented in appendix 2.

### Data collection process/ Data items (appendix 3)

### Risk of bias in individual studies (appendix 4)

#### Outcome measures

*Primary outcome:* aesthetic assessment of root coverage outcomes at patient level using a well-defined patient evaluation and/or a standardized clinical assessment.

*Secondary outcome:* professional evaluation of aesthetic outcomes using standardized approaches.

Aesthetic evaluations using empiric or unclear approaches were not considered. In order to reduce the possible source of heterogeneity, only standardized score systems to evaluate aesthetics used in at least 3 different studies were considered for quantitative data analysis.

#### Bayesian network meta-analysis (BNM)

It was planned a priori to create a network of RCTs involving single recessions and single plus multiple recessions (meaning studies treating both single and multiple recessions) while studies involving surgical techniques specifically aimed at treating multiple recessions only were considered separately.

Outcomes along with respective standard deviations were extracted from each primary study and expressed in percentage (%). Difference between treatments was calculated for each comparison within individual studies. For split-mouth studies, when standard deviation of the mean difference

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3 was not reported, it was calculated by individual patient data (IPD) if available. When several time  
4 point follow-up measures longer than 6 months were reported for the same sample in the same or  
5 different studies, the early report was selected to retrieve information regarding aesthetic outcomes,  
6 even if also the long-term follow-up was checked to retrieve possible additional outcomes.  
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12 A BNM model was then constructed for each of the outcome variables allowing for the inclusion of  
13 all the possible treatment comparisons. Direct comparisons of treatments as well as indirect  
14 comparisons were analysed in the same framework. Information from direct and indirect evidence  
15 can be combined in a NM only in the case that each treatment/trial is part of a connected network  
16 (i.e each trial shares at least a common comparator treatment). The description of the method and  
17 model specification details is presented in Appendix 5.  
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## RESULTS

The electronic searches provided a total of 47 abstracts published from May 2013 until January 2016. Subsequently, after full-text reading, 9 articles were selected. By merging these 9 articles with the references of the previous SRs (Cairo et al. 2014; Graziani et al. 2014) a total of 18 articles was obtained. At this time, two articles were excluded since a long-term study (McGuire et al. 2012; Cairo et al. 2015) of a previously published short-term trials (McGuire & Nunn 2003; Cairo et al. 2012). Finally, 16 RCTs met inclusion criteria (Table 1). In one case (Aroca et al. 2013), the contact of the authors provided further information regarding outcomes variables. The PRISMA flow chart of the screening and selection process is presented in fig. 1. Rejected studies at this stage and rationale for rejection are listed in Appendix 6 and 7 (supplementary materials).

## RESULTS OF THE ANALYSIS

### Study characteristics and Risk of bias within studies (appendix 8)

#### Results of the analysis

Among the applied scoring methods to assess aesthetic outcomes, only VAS Est at patient level and RES at professional level were used in at least 3 different studies to be considered for inclusion in a BNM model. Regarding the two clusters of studies considered (single plus single/multiple recessions (S/M Rec) treatment and multiple recessions (MRec) only, VAS Est was applied in 5 RCTs on S/M Rec (Cairo et al. 2012; Zucchelli et al. 2012; Roman et al. 2013; Salhi et al. 2014; Zuhr et al. 2014), but data for meta-analysis were reported in 4 RCTs (Cairo et al. 2012; Zucchelli et al. 2012; Roman et al. 2013; Zuhr et al. 2014). Only 2 RCTs on MRec applying VAS Est were available (Aroca et al. 2013; Zucchelli et al. 2014).

RES was applied in 5 RCTs regarding S/M Rec (Jhaveri et al. 2000; Cairo et al. 2012; Roman et al. 2013; Zuhr et al. 2014; Milinkovic et al. 2015) and in 2 RCTs on MRec (Ahmedbeyli et al. 2014; Ozenci et al. 2015). The study by Milinkovic et al. 2015 could not be included in the quantitative data analysis for S/M Rec group as the statistical tests performed in the original paper were not adjusted for the split-mouth design and did not take into account the within-patient correlation. The



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3 studies available for the MRec group were only 2 (Ahmedbeyli et al. 2014 and Ozenci et al. 2015),  
4 each one testing a different treatment comparison. Therefore no quantitative data analysis was  
5 performed.  
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11 Therefore a BNM regarding VAS Est for S/M Rec and a BNM regarding were performed. Studies  
12 included in the BNM models are presented in table 2. The results of the analysis are then reported in  
13 table 3 and presented separately for VAS Est and RES.  
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### 21 *Network Geometry*

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23 Two different network geometries were used in order to describe the architecture of evidence for  
24 each of the outcome variables (VAS Est and RES). Network graphs are reported in Fig. 2. Both the  
25 network identified CAF+CTG as the reference treatment. Only 1 RCT was available for each direct  
26 comparison  
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### 29 **VAS Est**

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33 Data from 3 studies included in this systematic review were available for the NM for the  
34 VAS Est outcome variable regarding the treatment of S/M Rec:  
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37 • Zucchelli et al. (2010) considered the comparison between CAF+CTG (test) vs.  
38 LPF (control). The mean VAS Est was  $91.2 \pm 9.3$  for the test group while  $89.6 \pm 7.9$   
39 for the control group. Individual patient data (IPD) available in the paper were re-  
40 analysed to obtain mean difference for VAS Est.  
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44 • Cairo et al. (2012) considered the comparison between CAF+CTG (test) vs. CAF  
45 (control). The mean VAS Est was  $80.3 \pm 15$  for the test group while  $75.0 \pm 14.5$  for  
46 the control group. Individual patient data (IPD) were provided by the author and re-  
47 analysed to obtain mean difference for VAS Est.  
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51 • Roman et al. (2013) considered the comparison between CAF+CTG+EMD vs.  
52 CAF+CTG. The mean VAS Est was  $87.0 \pm 16$  for the test group while  $89.5 \pm 15$  for  
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3 the control group. Average data from each treatment group available in the paper  
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5 were re-analysed to obtain mean difference for VAS Est.  
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10 The final mean VAS Est considering the 3 studies enclosed in the BNM was 85,4.  
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13 The study by Zuhr et al. (2013) was similarly not included in the present BN for the reasons  
14 presented above. The mean VAS est for the TT+CTG group was  $9.2 \pm 1.4$  while  $9.1 \pm 1.1$  in the  
15 CAF+EMD group considering a 0 to 10 VAS.  
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21 The treatment alternatives considered for the analysis were 4:

- 22 • CAF
- 23 • CAF+CTG
- 24 • CAF+CTG+EMD
- 25 • LPF

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29 With 4 treatment options, a total of 6 comparisons were possible.

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31 Three direct comparisons were based on data from RCTs:

- 32 • CAF+CTG vs. LPF 1 RCT (50 Patients)
- 33 • CAF+CTG vs. CAF 1 RCT (29 Patients)
- 34 • CAF+CTG vs. CAF+CTG+EMD 1 RCT (42 Patients)

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38 Three comparisons were never directly tested in RCTs:

- 39 • LPF vs. CAF
- 40 • LPF vs. CAF+CTG+EMD
- 41 • CAF vs. CAF+CTG+EMD

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47 When compared to CAF alone, the greatest mean differences for VAS Est were achieved by  
48 the combined CAF+CTG treatment (-5.42, 90%CrI: [-14.56; 3.73]), and then by LPF (-3.79,  
49 90%CrI: [-13.78; 6.16]) and CAF+CTG+EMD (-2.93, 90%CrI: [-9.08; 14.86]). The CAF+CTG  
50 combination resulted to be slightly better than CAF+CTG+EMD (-2.49, 90%CrI: [-10.31; 5.29])  
51 and than LPF (-1.63, 90%CrI: [-5.65; 2.35]), but the estimated difference did not result to be either  
52 statistically or clinically relevant.  
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3 The BNM model produced estimates also on the LPF vs. CAF+CTG+EMD, but the  
4 estimated difference did not result to be either statistically or clinically significant.

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6 All pair-wise comparisons for VAS Est are reported in Table 3.

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8 The *Ranking* of treatments by effectiveness was the following: 1. CAF+CTG (posterior  
9 median rank = 1.71); 2. LPF (2.45); 3. CAF+CTG+EMD (2.61); 4. CAF (3.23) (Table 4, Fig. 4-  
10 additional material).

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12 The surgical procedures with the highest probability (Pr) of being the *Best* treatments were  
13 the combined CAF+CTG treatment (Pr = 44%) and CAF+CTG+EMD (Pr = 26%) (Table 4, Fig. 4-  
14 additional material). The largest SUCRA was obtained for CAF+CTG (0.75). The performance of  
15 LPF and CAF+CTG+EMD was similar (SUCRA= 0.52 and 0.46, respectively). (Fig. 3)

## 22 23 RES

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25 Data from 3 out of the 14 studies included in this systematic review were available for the  
26 BNM for the RES outcome variable regarding the treatment of S/M Rec:

- 27  
28 • Jhaveri et al. (2010) considered the comparison between CAF+ADM with AF (test)  
29 vs CAF+CTG. The authors reported  $8.1 \pm 2.3$  of mean final RES for test group while  
30  $7.9 \pm 1.3$  for the control group. Individual patient data (IPD) available in the paper  
31 were re-analysed to obtain mean difference for RES.
- 32  
33 • Cairo et al. (2012) considered the comparison between CAF+CTG (test) vs. CAF  
34 (control). The mean RES was  $7.6 \pm 1.7$  for the test group while  $6.7 \pm 1.5$  for the  
35 control group. Individual patient data (IPD) were provided by the author and re-  
36 analysed to obtain mean difference for RES.
- 37  
38 • Roman et al. (2013) considered the comparison between CAF+CTG+EMD (test) vs.  
39 CAF+CTG (control). The mean RES was  $8.6 \pm 1.5$  for the test group while  $9.0 \pm 1.1$   
40 for the control group. Average data from each treatment group available in the paper  
41 were re-analysed to obtain mean difference for RES.

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43 The final mean RES score considering the 3 studies enclosed in the BNM was 7,9.

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45 The study by Zuhr et al. (2013), investigating tunnel technique with connective tissue graft  
46 (TT+CTG) and coronally advanced flap with enamel matrix derivative (CAF+EMD), could not be  
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3 included in the Network Meta-analysis model for RES, as neither these surgical procedures were  
4 tested in the trials included in the network. Zuhr et al. reported mean RES of  $9.1 \pm 0.8$  for TT+CTG  
5 group and  $6.9 \pm 2.3$  for CAF+EMD group.  
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9 The treatment alternatives considered for the analysis were 4:

- 10 • CAF
- 11 • CAF+CTG
- 12 • CAF+CTG+EMD
- 13 • CAF+ADM with Autogenous Fibroblasts (AF)

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15 With 4 treatment options, a total of 6 comparisons were possible.

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17 Three direct comparisons were based on data from RCTs:

- 18 • CAF+CTG vs. CAF+ADM with AF 1 RCT (10 patients)
- 19 • CAF+CTG vs. CAF 1 RCT (29 Patients)
- 20 • CAF+CTG vs. CAF+CTG+EMD 1 RCT (42 Patients)

21  
22 Three comparisons were never directly tested in RCTs:

- 23 • CAF vs. CAF+ADM with AF
- 24 • CAF+CTG+EMD vs. CAF+ADM with AF
- 25 • CAF vs. CAF+CTG+EMD

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27 When compared to CAF alone, the greatest mean differences for RES were achieved by the  
28 combined CAF+ADM with AF treatment ( $-1.06$ , 90%CrI:  $[-2.23; 0.10]$ ), and then by CAF+CTG ( $-$   
29  $0.87$ , 90%CrI:  $[-1.83; 0.10]$ ). The CAF+ADM with AF combination resulted to be slightly better  
30 than CAF+CTG ( $0.20$ , 90%CrI:  $[-0.45; 0.83]$ ), but the estimated difference did not result to be  
31 either statistically or clinically significant.  
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34 The BNM model produced estimates also on the following treatments: CAF+CTG vs.  
35 CAF+CTG+EMD, CAF+ADM with AF vs. CAF+CTG+EMD and CAF vs. CAF+CTG+EMD.  
36 However the estimated differences did not result to be either statistically or clinically significant.  
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38 All pair-wise comparisons for RES are reported in Table 3.

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40 The *Ranking* of treatments by effectiveness was the following: 1. CAF+ADM with AF  
41 (posterior median rank = 1.51); 2. CAF+CTG (1.92); 3. CAF+CTG+EMD (2.97); 4. CAF (3.60)  
42 (Table 4, Fig. 1).  
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3 The surgical procedures with the highest probability (Pr) of being the *Best* treatments were  
4 the combined CAF+ADM with AF treatment (Pr = 64%) and CAF+CTG (Pr = 24%) (Table 4, Fig.  
5 5-additional material).  
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8 The posterior cumulative ranking probabilities for each treatment in the network are  
9 represented in Fig 3. For treatment *i* the Surface under the Cumulative Ranking Curve (SUCRA)  
10 can be interpreted as the average proportion of treatments worse than *i*. The largest SUCRA was  
11 obtained for CAF+ADM (0.83) and for CAF+CTG (0.69).  
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For Peer Review

## DISCUSSION

### *Summary of evidence*

The purpose of the present study was to systematically review the literature on the efficacy of PPS procedures to improve esthetics at professional and patient levels. The primary outcomes showed that surgical procedures are able to improve aesthetic outcomes at patient level. Secondary outcomes demonstrated that PPS is also able to improve aesthetics rated by a professional score as RES. In the present study a BNM was applied in order to create a network of interventions including both direct and indirect comparisons among different trials. The main advantage of using a BNM model relies on the opportunity of estimating the *Best* treatment, i.e. the probability that each of the root coverage procedures is the best (Lu & Ades 2004,2006) and establishing an efficacy *Ranking* among the tested treatments by calculating the posterior distribution of the rank of each treatment and its mean.

The primary aim of the present BNM was to explore the effect of PPS in term of self-perceived aesthetic satisfaction. A recent survey (Kim et al. 2014), assessing professional and patient satisfaction after root coverage suggested that aesthetic evaluation by periodontist may not always be consistent with patient satisfaction. In fact, patient perception seems to be strongly related with some RES variables assessing the integration of soft tissue with adjacent tissue while professional appraisal seems to be more influenced by the amount of root coverage (Kim et al. 2014). This finding suggests that several factors including scar tissue formation and gingival colour may influence final patient satisfaction more than the pure root coverage outcomes. Among the possible scores to rate patient satisfaction, the visual analogue scale (VAS) obtained increased interest in recent years to quantify patient outcomes after periodontal therapy (Tonetti et al. 2014). This is a psychometric response scale used in questionnaires for collecting subjective characteristics that cannot be directly measured; VAS value is quantified by indicating a position along a continuous line between two end-points. In the current SR, three RTCs were finally available to perform a NM on patient aesthetic satisfaction after treatment of single and single plus multiple recessions. Interestingly, surgical procedures enclosed in the BNM were associated with a high mean value of VAS est (85.4) thus suggesting that different techniques may provide high final patient satisfaction. The surgical procedures with the highest probability of being the *Best* treatments in term of aesthetics were CAF+CTG treatment (Pr = 44%) and CAF+CTG+EMD (Pr = 26%). This finding

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3 suggests that more effective techniques using CTG in term of clinical efficacy for root coverage  
4 (Cairo et al. 2008; Buti et al. 2011; Buti et al. 2013, Cairo et al. 2014) were also associated with  
5 higher patient satisfaction. On the other hand, it should be kept also in mind that final satisfaction is  
6 not able to capture the possible discomfort after surgery. In fact, the application of CTG requires a  
7 second surgical procedure at the palatal site with longer surgical time, higher post-operative  
8 morbidity and analgesics use (Cortellini et al. 2009; Cairo et al. 2012). Conversely, further studies  
9 evaluating the final aesthetic satisfaction in relation to the specific surgical procedure are mandatory  
10 in order to evaluate possible psychological and socio-economic factors that may influence the  
11 reported outcomes at patient level.  
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21 The second aim of the study was to explore if PPS achieved aesthetic outcomes rated by  
22 professional scores at the operator level. In the modern clinical research the position of the gingival  
23 margin after surgery may be considered restrictive and not be adequate by it self for rating the  
24 overall aesthetic outcome of the treatment. To overcome this limitation, the Root coverage  
25 Aesthetic Score (RES) was introduced. This score is based on the evaluation of five variables: the  
26 level of the gingival margin, marginal contour, soft tissue surface, position of the MGJ, and gingival  
27 colour. RES values vary from 0 (final residual recession equal to or higher than the baseline  
28 recession) to 10 (CRC associated with the fulfilment of the other four variables). A large multi-  
29 centre study among expert periodontists showed that RES score is a reliable method to assess final  
30 aesthetics 6 months after periodontal plastic surgery with a total inter-rater agreement of 0.92,  
31 indicating an almost perfect agreement (Cairo et al. 2010). The present BMN showed that PPS  
32 techniques are associated with high values of RES score after treatment considering the cluster of  
33 studies treating single and single plus multiple recessions; the final mean RES score considering the  
34 3 studies enclosed in the BNM was 7,9 thus suggesting that different techniques are associated with  
35 high values of RES score. In the present BMN three combinations of the CAF techniques  
36 (CAF+CTG, CAF+CTG+EMD, CAF+ADM with AF) were more effective than CAF alone.  
37 However, the estimated differences were not significant. The surgical procedures with the highest  
38 probability to be *Best* treatments were the combined CAF+ADM with AF treatment and  
39 CAF+CTG, thus confirming that grafts improve the effectiveness of CAF alone (Cairo et al. 2008,  
40 Cairo et al. 2014). Conversely, it should be taken in mind that RES score combined both  
41 quantitative (amount of root coverage) and qualitative (soft tissue characteristics) variables; the  
42 current investigation is not able to identify specific interactions between the type of surgical  
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3 procedure and specific aesthetic impairment after treatment (e.g. persistence of scar tissue or  
4 alteration in colour). Further specific studies investigating associations between patient- and  
5 surgical-related factors and final aesthetic outcomes are strongly recommended to identify factors  
6 predicting outcomes after surgery.  
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11 The present BNM showed that all RTCs enclosed in the final analysis are recently published (2001-  
12 2014) thus suggesting that critical assessment of aesthetic outcomes at both clinical and patient  
13 level is a very modern approach in clinical research. This temporal trend may be due to the fact that  
14 changing in paradigms in classical mucogingival surgery started in middle of 90's moving from  
15 increasing dimension of residual gingiva to the modern periodontal plastic surgery procedure aimed  
16 at obtaining root coverage and soft tissue aesthetics (Miller 1993, AAP 1996). In addition, current  
17 patients usually show stringent aesthetic demands and, as consequence, surgical procedures have  
18 become more sophisticated not only to obtain satisfactory amount of root coverage but also soft  
19 tissue anatomy comparable to and indistinguishable from adjacent tissue (Cairo et al. 2009). The  
20 development of specific surgical instruments, sutures and enhancement systems (Burkhardt & Lang  
21 2005) may represent supporting tools for clinicians to improve final aesthetics of modern  
22 periodontal plastic surgery.  
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### 32 *Limitations*

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36 In interpreting the results of the present systematic review, it should be taken into account the  
37 limited number of trials available for the analysis and the fact that no more than one study included  
38 in the BNM provided data for the same pair-wise treatment comparison. The lack of information on  
39 heterogeneity and inconsistency does not imply absence of these sources of variability.  
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### 48 **Conclusions**

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50 | On the basis of the obtained data and considering the limited evidence available, it appears that:  
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53 i) PPS is associated with high patient satisfaction rated by VAS values indicating that CAF+CTG  
54 with or without the adding of EMD is associated with highest aesthetic satisfaction after healing.  
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3 ii) PPS improve soft tissue aesthetics rated by means Root Coverage Aesthetics Score; in particular  
4 grafting CAF is associated with higher values of RES score than CAF alone.  
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10 **Indications for future research**

11 i) Increased number of RCTs evaluating the patient satisfaction after root coverage procedures is  
12 suggested  
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14 ii) The potential effect of patient satisfaction and preference should be evaluated in further studies  
15 dealing on periodontal plastic surgery  
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18 iii) Increased number of RCTs evaluating the aesthetic outcomes of root coverage procedures using  
19 professional methods is suggested  
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**Tables:**

Table 1. RCTs presenting evaluation of aesthetic outcomes included in the SR

Table 2. Studies included in the Network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single and multiple recessions.

Table 3. Results of the Bayesian network meta-analysis for RES and VAS Est outcomes for studies treating single recessions and single plus multiple recessions.

Table 4. *Ranking* in efficacy and *Best* for RES and VAS Est outcomes for single recessions.

**Figures legend:**

Fig. 1: PRISMA flow chart

Fig. 2: Network plot for RES (a) and VAS Est (b) showing: direct pair-wise comparisons (continuous lines); both direct and indirect pair-wise comparisons (dotted lines); risk of bias estimation (green color = low risk; yellow = moderate risk; and red = high risk of bias). Nodes are weighted according to the number of studies including the respective intervention. Edges are weighted according to the number of studies including the respective comparison.

**Fig. 3:** Cumulative ranking curves and surfaces under these curves (SUCRA) for RES and VAS Est.

**Fig. 4 (additional material).** Ranking Graph for VAS Est: Treatments with the higher ranking are positioned on the left side of the graph: as lower the values of the ranking as higher the position of the treatment in the grading of efficacy (i.e.: CAF+CTG is the treatment with the highest ranking). The bubble size is directly proportional to the probability that the treatment is the *Best*: as greater the bubble as higher the *Best*

**Fig. 5 (additional material).** Ranking Graph for RES: Treatments with the higher ranking are positioned on the left side of the graph: as lower the values of the ranking as higher the position of the treatment in the grading of efficacy (i.e.: CAF+ADM with AF is the treatment with the highest

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3 ranking). The bubble size is directly proportional to the probability that the treatment is the *Best*: as  
4 greater the bubble as higher the *Best* (i.e.: CAF+ADM with AF is the treatment with the highest  
5 *Best*).  
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### 13 **Additional text material**

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16 Appendix 1-Study selection

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18 Appendix 2-Information sources and Search

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20 Appendix 3-Data collection process

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22 Appendix 4-Risk of bias in individual studies

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24 Appendix 5.Bayesian network meta-analysis

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26 Appendix 6- Rejected studies.

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28 Appendix 7-references excluded studies

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30 Appendix 8-Study characteristics and Risk of bias within studies  
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