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Original Article

Treating periodontal disease in patients with myocardial infarction: A randomized clinical trial

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ABSTRACT

Background: Periodontitis has been associated with coronary artery disease, but the impact of a periodontal treatment on the endothelial function of patients with a recent ST-segment elevation myocardial infarction (STEMI) was not investigated.

Methods: Randomized controlled trial (NCT02543502). Patients admitted between August 2012 and January 2015 were included. Patients were screened during the index hospitalization for STEMI, and those with severe periodontal disease were randomized 2 weeks later to periodontal treatment or to control. The primary endpoint of this trial was the between group difference in the variation of flow-mediated vasodilation (FMD) in the brachial artery assessed by ultrasound from baseline to the 6-month follow-up. Secondary outcomes were cardiovascular events, adverse effects of periodontal treatment and inflammatory markers.

Results: Baseline characteristics were balanced between patients in the intervention (n = 24) and control groups (n = 24). There was a significant FMD improvement in the intervention group (3.05%; p = .01), but not in the control group (−0.29%; p = .79) (p = .03 for the intergroup comparison). Periodontal treatment was not associated with any adverse events and the inflammatory profile and cardiovascular events were not significantly different between both groups.

Conclusions: Treatment of periodontal disease improves the endothelial function of patients with a recent myocardial infarction, without adverse clinical events. Larger trials are needed to assess the benefit of periodontal treatment on clinical outcomes.

Clinical trial registration: NCT02543502 (https://clinicaltrials.gov/ct2/show/NCT02543502?term=NCT02543502&rank=1).

1. Introduction

ST-segment elevation myocardial infarction (STEMI) still presents high morbidity and mortality even with optimized treatment [1,2]. Thus, identifying novel risk factors and new potential therapeutic strategies are needed. Periodontal disease has a high world prevalence, and has been associated with coronary artery disease (CAD) [1,3]. Periodontal disease is a complex condition caused by the presence of a bacterial biofilm that colonizes the teeth surfaces and provokes chronic gingival inflammatory response [4]. The biological plausibility of this association is based on immune and inflammatory responses that could contribute to atheroma formation, evolution and instability [5].

However, a cause and effect relationship between periodontal and coronary artery diseases has not been established. Several risk factors for periodontal disease, such as smoking, arterial hypertension, diabetes mellitus, obesity and poor treatment adherence, are also risk factors for CAD [6–8]. Another relevant factor is that the complexity of periodontal treatment raises difficulties on performing randomized studies with a high number of patients.

Endothelial dysfunction represents an important part on the

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atherogenic process, and it has been used as a surrogate endpoint in studies of patients with CAD [9–11]. A previous trial demonstrated significant benefit of periodontal treatment on improving endothelial function of individuals with severe periodontal disease, but without CAD [11]. The impact of a periodontal treatment on the endothelial function of patients with a recent ST-segment elevation myocardial infarction (STEMI) was not investigated, and it is the objective of the present study.

2. Materials and methods

This study was a randomized controlled parallel clinical trial, registered on www.clinicaltrials.gov under the number NCT02543502. The study was approved by the institutional review board, and all patients enrolled provided written informed consent. The authors are solely responsible for the design and conduct of the study, statistical analysis, drafting and editing of the paper, and approval of its final contents. This study was performed without extramural funding.

All consecutive patients with STEMI admitted to our institution between August 2012 and January 2015 were considered for the study. Patients were screened during the index hospital admission for STEMI by a cardiologist and a periodontist. The inclusion criteria were STEMI and severe periodontal disease. STEMI was defined as typical chest pain at rest associated with ST-segment elevation of at least 1 mm in 2 contiguous leads in the frontal plane or 2 mm in the horizontal plane, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block. Severe periodontal disease was defined by clinical attachment loss higher or equal to 4 mm and subgingival probing depth higher or equal to 6 mm in at least 5 teeth, associated to gingival bleeding in at least 8 teeth [12].

Exclusion criteria were age under 30 years old, HIV positive, chronic inflammatory diseases, neoplastic diseases, drug addiction, use of anticonvulsants, use of immune suppressants, pregnancy, lactation, significant dental loss (< 8 teeth remaining), long length of stay in the hospital (> 10 days), a new myocardial infarction after the index event and before randomization, stent thrombosis and refusal to sign the informed consent.

Patients randomized to the intervention group underwent thorough periodontal evaluation by a periodontist (ML) at the dentistry clinic. All permanent teeth except for the third molars were assessed with an odontoscope and a periodontal probe. Each tooth was examined in four sites (vestibular, distal, lingual and mesial), evaluating visible plaque, probing depth, bleeding on probing and insertion loss [13].

Patients in the intervention group received periodontal treatment, while patients randomized to the control group received no periodontal treatment. However, periodontal treatment was offered to the patients in the control group after the end of the study. The periodontal treatment was performed with a standard treatment sequence by the same periodontist (ML) at the dentistry clinic. In the first session, information on periodontal disease was provided to the patients, focusing on the importance of controlling supragingival bacterial biofilm for treatment success. Retentive plaque factors (dental calculus) were removed. Decay lesions were restored with provisional material; root remains were extracted, and badly adapted restorations were adjusted. Supragingival calculus was removed with periodontal curettes, followed by supragingival scaling and polishing with rubber cup, prophylactic paste, dental floss and/or interdental brush. Antibiotics prophylaxis was not used before the procedures [14]. Patients received instruction on personalized oral hygiene with multi bristle brush, toothpaste, dental floss and interdental brush.

The second session was scheduled to occur fourteen days after the first appointment. Subgingival root and scaling were initiated with periodontal curettes and files under local anesthesia for a maximum period of four weeks. Further sessions were scheduled as needed. By the end of each visit, patients received professional plaque removal and oral hygiene reinforcement according to individual needs in order to motivate and obtain effective behavioral changes. After 90 days, patients were reassessed for dental hygiene check and additional professional plaque removal. A final complete periodontal examination was performed at 6 months after enrolment.

The primary endpoint of this trial was the between group difference in the variation of flow-mediated vasodilation (FMD) in the brachial artery assessed by ultrasound from baseline to follow-up. Flow-mediated vasodilation was measured to evaluate the arterial endothelium-dependent vasodilation using a high-resolution vascular ultrasound (EnVisor CHD; Philips, Bothell, WA, USA) and a 3–12 MHz linear-array transducer (L12–3, Philips, Bothell, WA, USA) [15]. Patients were submitted to a baseline and final evaluation, which were performed in triplicate by an experienced operator (TD). The evaluations were performed in the period of the morning after an 8-h fast, in controlled temperature (22 °C). After a ten-minute rest, images of the brachial artery were recorded with a linear transducer placed continuously over the antecubital fossa for one minute (basal). Flow measurements were continuously made with a Doppler wave pulse at an angle of 70°. The sphygmomanometer cuff was inflated to 50 mm/Hg above the systolic blood pressure for five minutes, and brachial artery diameter after 60 s of cuff deflation was compared to the basal diameter. The brachial artery diameter images at the end of diastole were digitalized and recorded in 3-s gaps, and analyzed offline using the equipment software. The increase of blood flow after cuff deflation was expressed as the reactive-hyperemia ratio.

Secondary outcomes were indices of periodontal health, inflammatory markers, and clinical outcomes. Safety outcomes were the incidence of clinically significant bacteremia and adverse cardiovascular events. Clinically significant bacteremia was defined as the occurrence of fever > 37.8 °C in the first 24 h following periodontal treatment. Cardiovascular events assessed were death, myocardial infarction, stent thrombosis and urgent revascularization. Myocardial infarction (MI) was defined by chest pain with elevation of serum biomarkers, with ST-segment elevation or new Q waves. Stent thrombosis was defined according to the Academic Research Consortium criteria [16]. Urgent revascularization was defined as an unplanned revascularization procedure in the first 30 days after the index STEMI, either by percutaneous coronary intervention (PCI) or coronary artery by-pass surgery, to treat recurrent myocardial ischemia. All cardiovascular events were centrally adjudicated by the study investigators (MS, AQ).

Serum levels of IL-1β, IL-6 and IL-10 were determined by the ELISA test, based on antigen-antibody interaction using commercial kits (Elabsciences), in accordance with the manufacturers' instructions. All samples were dosed in duplicate before periodontal treatment and at the 6-month follow-up (MK). The data are expressed as protein picograms per milliliter (pg/mL).

Sample size was estimated in 88 patients to detect a 1% difference in the flow-mediated dilation between the two study groups with an average standard deviation of 1.67%, for a two-sided $p < .05$ and 80% statistical power [11]. However, the recruitment rate was lower than initially expected due to a high percent of study patients with exclusion criteria and to logistical aspects. The operational aspects of systematically evaluating periodontal disease in patients hospitalized for an acute myocardial infarction were a challenge that was underestimated in the beginning of the study. For these reasons, the trial was interrupted prematurely after including 48 patients in a two and a half years period. We have performed a sensitivity analysis using an arbitrary penalty of a p value of 0.025 to account for this lower than initially projected statistical power, which was 67%.

We performed the baseline evaluation of FMD two weeks after hospital discharge in all patients. The randomization to the intervention or control group was performed after this evaluation with a computer-generated table (www.randomization.com). The control group did not receive any clinical intervention during the study period. Allocation of randomization was concealed, and it was done by one of the

investigators (IP).

Periodontal treatment was opened and performed by one of the investigators (ML). The evaluation of the endothelial function was performed by an investigator (TD) blinded to the treatment assignment. Other health care providers who were involved in patient care did not know about the patient treatment allocation.

Data were analyzed using SPSS 22. Categorical variables were presented as percent, and continuous variables as mean and standard deviation or median and interquartile range. All analyzes were based on the intention-to-treat principle. The *t*-test and the chi-square test were used to compare baseline variables between groups. The Mann-Whitney test was used to compare cytokine levels from baseline to 6-month follow-up. The t-test for paired samples was used to compare FMD before and after periodontal treatment. A generalized estimative equation with the Bonferroni method was applied to assess the statistical significance of the difference in the intergroup FMD variation, and the result was presented with confidence intervals. A two tailed $p < .05$ was considered statistically significant for all tests.

3. Results

The study flowchart is shown in Fig. 1. From the 632 individuals presenting with STEMI to our institution during the study period, 61 patients died, 228 patients did not have severe periodontal disease, 255 patients had significant dental loss and 37 patients were excluded for other reasons. One patient was screened for participation, but presented a new myocardial infarction after hospital discharge and before randomization, and therefore, was considered a screening failure.

The final study sample was comprised of 48 individuals. Baseline characteristics according to study treatment are shown in Table 1. Patients in the control group more frequently presented family history of CAD than patients in the treatment group, but all other characteristics were not statistically different between both groups. Table 2 shows angiographic and laboratorial variables, which were similar between patients assigned to periodontal treatment or control.

Table 3 shows the evaluation of periodontal status before treatment and at the 6-month follow-up. We observed statistically significant reductions in all indices after periodontal treatment: lower number of teeth with probing depth higher or equal to 4 mm, fewer teeth with clinical attachment loss higher or equal to 4 mm, less bleeding on probing and visible plaque.

Fig. 2 shows the effect of periodontal treatment on the primary study outcome. Flow-mediated dilation significantly improved in patients receiving periodontal treatment (from 9.0 ± 4.4% at baseline to

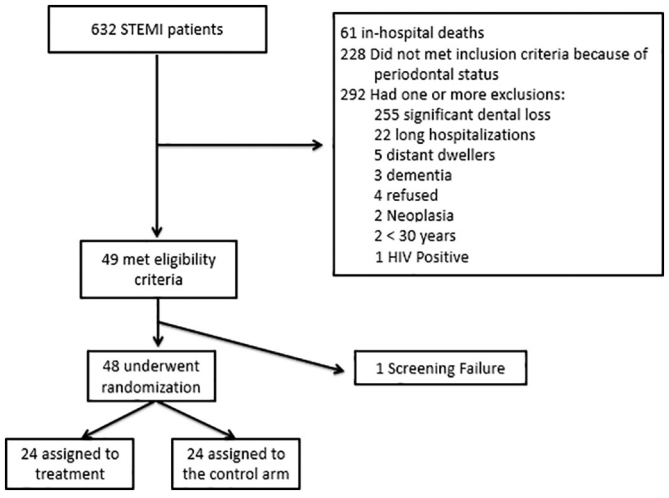

Fig. 1. Study flowchart. STEMI, ST-segment elevation myocardial infarction; HIV, Human Immunodeficiency Virus.

Table 1
Baseline characteristics.

Characteristic	Treatment (*n* = 24)	Control (n = 24)	*P*
Age, years	52.7 ± 9.3	54.6 ± 6.7	0.42
Male, %	68	75	0.52
Hypertension, %	71	75	0.74
Diabetes mellitus, %	33	21	0.33
Dyslipidemia, %	33	46	0.37
Smoking, %	78	90	0.30
Family history of CAD, %	8	33	0.03
Medical history			
PCI, %	21	33	0.33
CABG, %	4	0	0.75
Myocardial infarction, %	29	33	0.75
Congestive heart failure, %	8	4	0.55
Chronic renal failure, %	0	0	
Anterior MI, %	50	29	0.14
TIMI risk score	2.58 ± 1.62	2.15 ± 1.34	0.47
Delta T, hours	3.00 [1.00–4.78]	3.68 [2.71–5.76]	0.13
Door-to-balloon time, hours	1.00 [0.88–1.40]	1.05 [0.86–1.47]	0.11

CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting;MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

Table 2
Angiographic and laboratory characteristics.

Characteristic	Treatment (n = 24)	Control (n = 24)	*P*
Three-vessel disease, %	10	12	0.60
LAD involvement, %	43	26	0.22
Reference vessel diameter, mm	3.39 ± 0.76	3.16 ± 0.55	0.27
Lesion length, mm	16.7 ± 6.6	17.9 ± 9.0	0.67
TIMI grade 3 flow			
Pre, %	29	17	0.34
Post, %	95	91	0.52
Blush grade 3			
Pre, %	21	4	0.09
Post, %	79	78	0.94
Laboratory evaluation			
Blood glucose, mg/dl	142 ± 41	183 ± 82	0.08
Total cholesterol, mg/dl	196 ± 46	191 ± 42	0.74
HDL cholesterol, mg/dl	46 ± 20	42 ± 14	0.51
Triglycerides, mg/dl	145 ± 97	167 ± 102	0.52
C-reactive protein, mg/dl	0.34 [0.13–0.92]	0.52 [0.23–2.81]	0.22
Fibrinogen, mg/dl	271 ± 52	329 ± 113	0.19
Hematocrit, %	42 ± 4	41 ± 5	0.58
Hemoglobin, g/dL	14 ± 1	14 ± 1	0.42
Leukocytes, mm^3	11,907 ± 4688	12,196 ± 2883	0.85
Platelets, mm^3	241,800 ± 80,272	238,500 ± 46,949	0.88
Creatinine, mg/dL	0.93 ± 0.31	0.87 ± 0.15	0.49
Peak CK-MB, ng/mL	23 [7–52]	43 [11–87]	0.22
Peak US troponin, ng/mL	491 [88–4067]	1907 [1205–5998]	0.24

LAD, left anterior descending artery; TIMI, Thrombolysis in Myocardial Infarction; HDL, high-density cholesterol; CK-MB, creatine kinase-MB; US, ultra-sensitive.

Table 3
Indices of periodontal status at baseline and at the 6-month after enrolment in patients in the intervention group.

Indices (by teeth)	Baseline	6-month	P
Probing depth ≥ 4 mm	75%	11%	< 0.001
Clinical attachment loss ≥ 4 mm	90%	50%	< 0.001
Bleeding to probing	79%	17%	< 0.001
Visible plaque	77%	12%	< 0.001

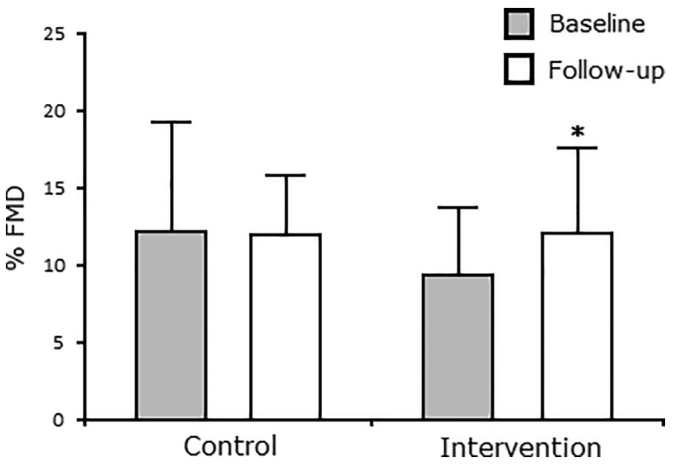

Fig. 2. Primary endpoint. Baseline and follow-up FMD values in the intervention and control group. FMD, flow-mediated dilation.

12.1 ± 5.6% at follow-up; $p = .01$), but it did not significantly change in patients in the control group (from 12.2 ± 7.2% at baseline to 11.9 ± 4.0% at follow-up; $p = .79$).

The difference in FMD variation between both groups was 3.4% (CI = 0.6–5.8%), and this was statistically significant according to the generalized estimative equation with the Bonferroni correction method ($p = .03$). In a sensitivity analysis with an alpha level of a 0.025 to account for the lower than projected statistical power, the p value was $p = .07$, which was not statistically significant but showed a strong trend towards the primary study hypothesis.

Regarding the inflammatory markers, we did not find statistically significant differences between baseline and 6-month values of interleukin-1B, interleukin-6 and interleukin 10 in either group (Fig. 3).

4. Discussion

In the present study, we have investigated the impact of periodontal treatment in patients with a recent myocardial infarction and severe periodontal disease. To our knowledge, this is the first study with patients with a recent myocardial infarction randomized to periodontal treatment or control. The main findings were that periodontal treatment significantly improved endothelial function of the brachial artery, without adverse clinical effects. Periodontal disease was previously associated with recurrent cardiovascular events in patients with a recent myocardial infarction [17,18] but no randomized clinical trial to date has assessed the effect of periodontal treatment on these patients. The post-infarction period is characterized by generalized inflammation and endothelial dysfunction [19,20] and an intervention improving endothelial function in this context may be clinically relevant. If confirmed by larger trials adequately powered to clinical outcomes, periodontal treatment could represent a novel approach to contribute to the improvement of cardiovascular outcomes in patients with a recent MI.

The strong association found between periodontal and cardiovascular diseases in epidemiological and cohort studies has raised the question if one disease influences the pathogenesis of the other [6,7]. Periodontal disease could stimulate or aggravate cardiovascular diseases by contributing to the inflammatory milieu. Because of the potential that preventing or treating periodontal disease could reduce cardiovascular events, this line of investigation has potentially important clinical implications. It has been shown that periodontal treatment improves lipid levels [21,22], inflammation [3,23] and endothelial function in individuals with periodontitis [11,24], but there are few trials including patients with established cardiovascular disease. It is important to evaluate the effectiveness of periodontal treatment in patients with established CAD, because there is an acute increase in inflammation and worsening of endothelial function in the first hours and days after periodontal treatment [11]. These effects have been attributed to the transient bacteremia that may occur when the mouth of a patient with periodontitis is surgically intervened. While in healthy subjects these physiological responses were not associated with overt clinical consequences, patients with cardiovascular diseases could be more sensitive to these effects, due to their own cardiovascular disorders and also to the frequent presence of other comorbidities.

Bokhari et al. randomized 317 patients with angiographically proven CAD to periodontal treatment or to a control group, and periodontal therapy significantly reduced systemic levels of C-reactive protein, fibrinogen and white blood cells [25]. No acute adverse events were reported associated with periodontal treatment. Offenbacher et al. included 302 patients with previous CAD in the PAVE Pilot study, and did not find any acute adverse events of periodontal treatment [26]. In the present study, we also did not find any acute adverse reactions associated with periodontal treatment.

The primary outcome in our study was the flow-mediated dilation of the brachial artery, which is a traditional surrogate endpoint in cardiovascular trials. Endothelial dysfunction plays an important role in atherosclerosis, since its inception to the advanced stages of the disease [19,27,28]. Ultrasound assessment of brachial artery FMD during reactive hyperaemia is a reproducible method for the assessment of endothelial dysfunction [29], and it is predictive of endothelial dysfunction in the coronary circulation [30]. Therefore, brachial artery FMD has emerged as an attractive noninvasive technique for the study of endothelial function as a marker of subclinical atherosclerosis. In a recent metanalysis with 35 FMD studies of 17,280 participants, it was found that 1% increase in FMD was associated with 12% less recurrent cardiovascular events [31].

In our study, periodontal treatment did not have a significant effect on circulating levels of inflammatory markers. This is in contrast with

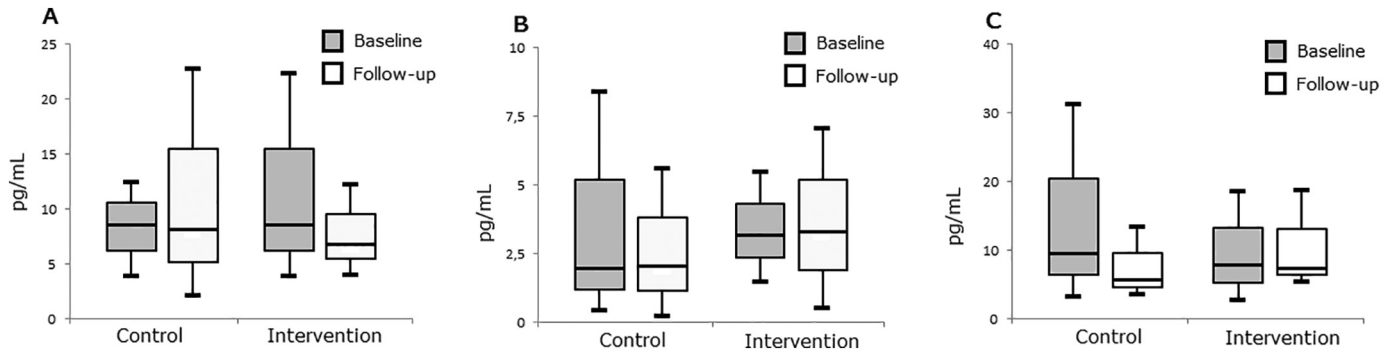

Fig. 3. A – Serum interleukin-1β levels at baseline and at the 6-month follow-up in patients in the intervention and control group. IL-1β, interleukin-1β. B – Serum interleukin-6 levels at baseline and at the 6-month follow-up in patients in the intervention and control group. IL-6, interleukin-6. C – Serum interleukin-10 levels at baseline and at the 6-month follow-up in patients in the intervention and control group. IL-10, interleukin-10.

previous studies, which reported that effective periodontal treatment is associated with lowering of mouth bacteria, and also of tissue and blood inflammation [3]. As the favorable effects of periodontal therapy on cardiovascular health have become increasingly evident, another aspect that needs to be addressed is if there is superiority of one specific type of periodontal treatment over the others. In our study, patients were treated in several sessions through a staged approach, but others have advocated treating periodontal disease in one single session [11,32]. The staged approach has the potential advantages of increasing patient adherence because of longer time to explain preventive measures, and also causes less acute trauma to the patient. It has already been tested in prior studies [22,31], but a direct comparison of the impact of these two approaches on cardiovascular markers or endothelial function is not available.

The major limitation of our study is the small number of patients. The operational aspects of systematically performing a periodontal evaluation in patients hospitalized for an acute myocardial infarction coupled with the high proportion of screening failures were not totally anticipated. Since this is the first study randomizing patients with myocardial infarction and severe periodontal disease during the initial hospitalization, the present report could be useful for the planning of future studies. The periodontal treatment was very effective in improving objective indices of periodontal status in the treatment group, but we did not perform periodontal evaluations in the control group to avoid co-intervention. The basal FMD values were higher in control group than in the intervention group and the final values were similar, but only the intervention group presented a significant improvement in FMD values. We have interpreted the improvement of FMD in the intervention group as the result of the biological effect of periodontal treatment, and lower values in this group as an unbalance in randomization due to a small sample, but a regression to the mean phenomenon cannot be totally excluded. This was a single center study done in Brazil, which may also limit the generalizability of our results to different practices. The lack of significant benefit of periodontal treatment on serum cytokines and clinical outcomes probably also probably reflects the low number of patients and lack of statistical power.

5. Conclusion

In this study, we demonstrate that treatment of periodontal disease significantly improves endothelial function in patients with a recent myocardial infarction and severe periodontal disease. Importantly, mouth instrumentation was not associated with adverse clinical outcomes in patients with a recent myocardial infarction and coronary stent implantation. If confirmed by larger trials, treatment of periodontal disease may emerge as a new approach to improve cardiovascular outcomes in the early post-infarct period.

Conflict of interest and source of funding

This study was funded by Instituto de Cardiologia do Rio Grande do Sul.

Disclosures for Dr. Lopes are available at https://dcri.org/about-us/conflict-of-interest. Dr. Quadros has received educational support and research grants from Medtronic Inc., Abbott Vascular, Terumo, Acrosstak and St Jude. The other authors report no potential conflicts of interest.

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