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REVIEW ARTICLE

Periodontitis and atherosclerotic cardiovascular disease: A critical appraisal

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1 | INTRODUCTION

The presence of periodontitis is increasingly recognized as an independent cardiovascular risk factor. For instance, the exploitation of digital data by artificial intelligence supports this contention (Boxes 1 and 2). On the occasion of the 2012 joint workshop on Periodontitis and Systemic Diseases organized by the European Federation of Periodontology (EFP) and the American Academy of Periodontology (AAP), Dietrich et al. systematically examined the epidemiological association between periodontitis and ASCVD.[1] Based on the 12 studies included in their systematic review, they concluded that there is an increased risk of ASCVD in patients with periodontitis compared with patients without periodontitis. In February 2019, a joint workshop organized by the EFP and the World Heart Federation (WHF) was held to review the relationship between periodontitis and cardiovascular diseases as observational studies supported the association between these two diseases.[2] The objective of this workshop was to update the evidence from the 2012 joint EFP and AAP workshop,[3] and three additional narrative reviews were conducted.[4–6] Therefore, there are already a large number of reviews of the literature dealing with this topic, and it is not our intention to add a new review to what can already be found elsewhere. The purpose of this article is to provide a critical appraisal of the current knowledge considering recent data. Consequently, the relevance of the articles on which the main sections of this narrative review are based relies upon our own judgment.

We also decided to highlight and update the association between periodontitis and arterial hypertension. Arterial hypertension (AH) is one of the major modifiable risk factors for cardiovascular diseases/events.[7,8] In 2017, the Global Burden of Disease study indicated that nonoptimal blood pressure leads to 10.4 million deaths and 218 million lost healthy life years each year, making AH one of the leading risk factors of all-cause mortality worldwide.[9] Because of its high prevalence, with approximately one in four adults being affected,[10] AH is targeted by primary prevention guidelines recommending the lowering of blood pressure through lifestyle modification and medical therapy to reduce ASCVD risk.[11–13]

BOX 1 Is periodontitis an independent contributing factor to cardiovascular risk? The answer of the AI (Chat GPT) (September 13, 2023).

Periodontitis, a severe form of gum disease, has been associated with an increased risk of cardiovascular disease in various studies and research findings. While it's not necessarily considered an independent contributing factor, there is evidence to suggest that periodontitis may contribute to cardiovascular risk when other risk factors are present.

The exact mechanisms underlying the link between periodontitis and cardiovascular disease are not fully understood, but several theories have been proposed:

- Inflammation: Periodontitis is characterized by chronic inflammation in the gums, which can lead to the release of inflammatory markers into the bloodstream. These markers may contribute to the development and progression of atherosclerosis (hardening and narrowing of the arteries), which is a key component of cardiovascular disease.
- Bacterial Spread: The bacteria associated with periodontitis can enter the bloodstream through inflamed gum tissue and potentially contribute to the formation of arterial plaques, further increasing the risk of cardiovascular events.
- Systemic Inflammation: Chronic inflammation in the body, including that caused by periodontitis, can have systemic effects that impact various organs and systems, including the cardiovascular system.
- Shared Risk Factors: Periodontitis and cardiovascular disease share common risk factors such as smoking, diabetes, and obesity. These risk factors can increase the likelihood of both conditions occurring simultaneously.

While there is evidence to suggest an association between periodontitis and cardiovascular risk, it's essential to understand that this link does not imply causation. It means that individuals with periodontitis may have a higher likelihood of developing cardiovascular disease, but other risk factors and genetic predispositions also play a role.

It's crucial to maintain good oral hygiene, including regular dental check-ups and proper gum care, as a part of overall health management. Additionally, if you have periodontitis or are at risk for cardiovascular disease, it's advisable to discuss your concerns with both a dentist and a healthcare provider to develop a comprehensive prevention and treatment plan.

The outline of this article follows a classical approach to identifying the impact of one disease on another. We have attempted to answer the following questions:

1. Is there an association between periodontitis and ASCVD?
2. Is this association supported by a plausible biological link?
3. Does periodontal therapy have an impact on the ASCVD risk?
4. Is there a causal relationship between periodontal disease and ASCVD?
5. What are the clinical and public health implications of the current knowledge on this topic?
6. What are the recommendations for future research?

A quantitative evaluation of the literature dealing with the periodontal systemic connection clearly indicates that leaving aside cancer and diabetes, cardiovascular diseases are at the forefront. A basic unfiltered search on PubMed* using the Boolean operator "AND" to link "periodontitis" and "cardiovascular diseases" retrieves 4256 papers at the time of writing this article (Figure 1A). Similarly, a qualitative approach to the literature, that is, when "clinical trial" is selected as a filter, shows 112 articles, which ranks the number of clinical trials addressing the relationship between periodontitis and cardiovascular disease second only to diabetes (216 articles) (Figure 1B). This informal analysis of the literature reflects the importance that this field of investigation has acquired in recent years, with a peak in 2014 (Figure 2). The following reasons may explain this:

1. ASCVD remains the leading cause of both death and disability.
2. Standard modifiable cardiovascular risk factors (SMuRFs), that is, hypertension, diabetes, hypercholesterolemia, and smoking as well as other traditional risk factors (age, sex, BMI, and physical activity) alone do not explain the incidence of fatal and nonfatal cardiovascular events such as myocardial infarction and ischemic stroke.[14]
3. Periodontitis is a highly prevalent noncommunicable chronic disease.[15]
4. Periodontitis is an inflammatory disease.
5. The plausibility of the biological link between periodontal inflammation and cardiovascular risk has been demonstrated.
6. Periodontitis is easily preventable.
7. Treatment of periodontitis improves metabolic and vascular parameters as well as decreasing systemic inflammatory markers.

Taken together, the above suggests that periodontitis may be a nontraditional risk factor for ASCVD.

1.1 | Historical context

The history of the oral/cardiovascular link is not a love story. In the past, the sole purpose of medicine was to cure the sick, that is, to

*https://pubmed.ncbi.nlm.nih.gov/.

BOX 2 What is the evidence pointing at a role for periodontitis in cardiovascular diseases? The answer of the AI (Bing AI) (September 13, 2023).

There is some evidence that suggests a possible link between periodontitis and cardiovascular diseases, but the exact nature and mechanisms of this association are still unclear. Some of the evidence pointing at a role for periodontitis in cardiovascular diseases are:

Periodontitis is a chronic inflammatory disease that affects the gums and the supporting tissues of the teeth. It is caused by a specific group of bacteria that can invade the bloodstream and trigger an immune response. This can lead to systemic inflammation and oxidative stress, which are known risk factors for cardiovascular diseases (1, 2).

Periodontitis can also increase the levels of certain inflammatory mediators in the blood, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha). These mediators can promote the formation and instability of atherosclerotic plaques, which are the main cause of coronary artery disease, stroke, and peripheral artery disease (1–3).

Periodontitis may also affect the endothelial function of the blood vessels, which is essential for maintaining vascular health and preventing thrombosis. Periodontal bacteria or their products can impair the production of nitric oxide (NO), a vasodilator that regulates blood pressure and prevents platelet aggregation. This can lead to endothelial dysfunction and increased risk of cardiovascular events (2, 3).

Periodontitis may also have an indirect effect on cardiovascular diseases by influencing other risk factors, such as diabetes, hypertension, dyslipidemia, obesity, and smoking. Periodontitis can worsen the glycemic control and insulin resistance in diabetic patients, increase blood pressure and cholesterol levels, induce weight gain and adipose tissue inflammation, and reduce the effectiveness of smoking cessation interventions. These factors can increase the cardiovascular risk in patients with periodontitis (1–3).

However, it is important to note that this evidence is mostly based on observational studies, which cannot establish a causal relationship between periodontitis and cardiovascular diseases. There may be other confounding factors that influence both conditions, such as genetic predisposition, lifestyle habits, socioeconomic status, and access to health care. Therefore, more randomized controlled trials are needed to confirm the effect of periodontal treatment on cardiovascular outcomes, (1–3).

Source: Conversation with Bing, September 13, 2023.

(1) https://www.health.harvard.edu/heart-health/gum-disease-and-heart-disease-the-common-thread

(2) https://www.frontiersin.org/articles/10.3389/fcvm.2020.625579/full

(3) https://link.springer.com/chapter/10.1007/978-3-030-96881-6_14

(4) https://www.efp.org/fileadmin/uploads/efp/Documents/Campaigns/Perio_and_Cardio/Scientific_report/consensus-report.pdf

(5) https://www.frontiersin.org/research-topics/55985/periodontitis-and-cardiovascular-disease-shared-clinical-challenges-in-patient-care

(6) https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-020-01356-4 (5) Periodontitis and Cardiovascular Diseases. Consensus Report. https://pubmed.ncbi.nlm.nih.gov/32489774/ Accessed March 2, 2023.

treat the disease. The question then was: "can dentists cure systemic diseases other than oral diseases by treating oral diseases?"

In 1912, Franck Billings argued that the extraction of "diseased" teeth could cure infections of a distant organ.[16] Therefore, all infected teeth should be extracted, as stated by Weston Andrew Price 13 years later.[17] This was the historical "focal infection theory". Thus, in North America, between 1930 and 1950, thousands of individuals were left toothless because of multiple tooth extractions driven by the focal infection theory. It was not until 1952, more than 25 years after the article of W.A. Price, that an editorial of the Journal of the American Medical Association reported that many patients had not been cured of their symptoms by removing their infected teeth, noting that "*Many patients with diseases presumably caused by foci of infection have not been relieved of their symptoms by removal of the foci, many patients with these same systemic diseases have no evidence of a focus of infection, foci of infection are as common in apparently healthy persons as in those with disease*".[18]

Because of the focal infection theory, for more than 35 years, between 1952 and 1989, the scientific community showed little interest in the relationship between oral diseases and the rest of the body, apart from subacute infective endocarditis, which is a rare disease usually caused by streptococcal bacteria. Regarding the incidence of infective endocarditis, in Western Europe and high-income North America, the age-standardized incident rate per 100 000 inhabitants in 2019 was 18.06 [$CI_{95\%}$ 15.32–21.34] and 14.31 [$CI_{95\%}$ −12.38–16.50], respectively. Concerning the deaths due to infective endocarditis in Western Europe and high-income North America, the age-standardized death rate (ASDR) per 100 000 population was 1.28 [$CI_{95\%}$ 0.63–1.57] and 1.36 [$CI_{95\%}$ 0.68–1.65], respectively.[10] In contrast, ASCVD (Figure 3), the leading cause of myocardial infraction (MI), cerebrovascular accident (CVA), and peripheral vascular disease (PAD), is extremely frequent in adults and begins in childhood[19] (Table 1). Indeed, in the

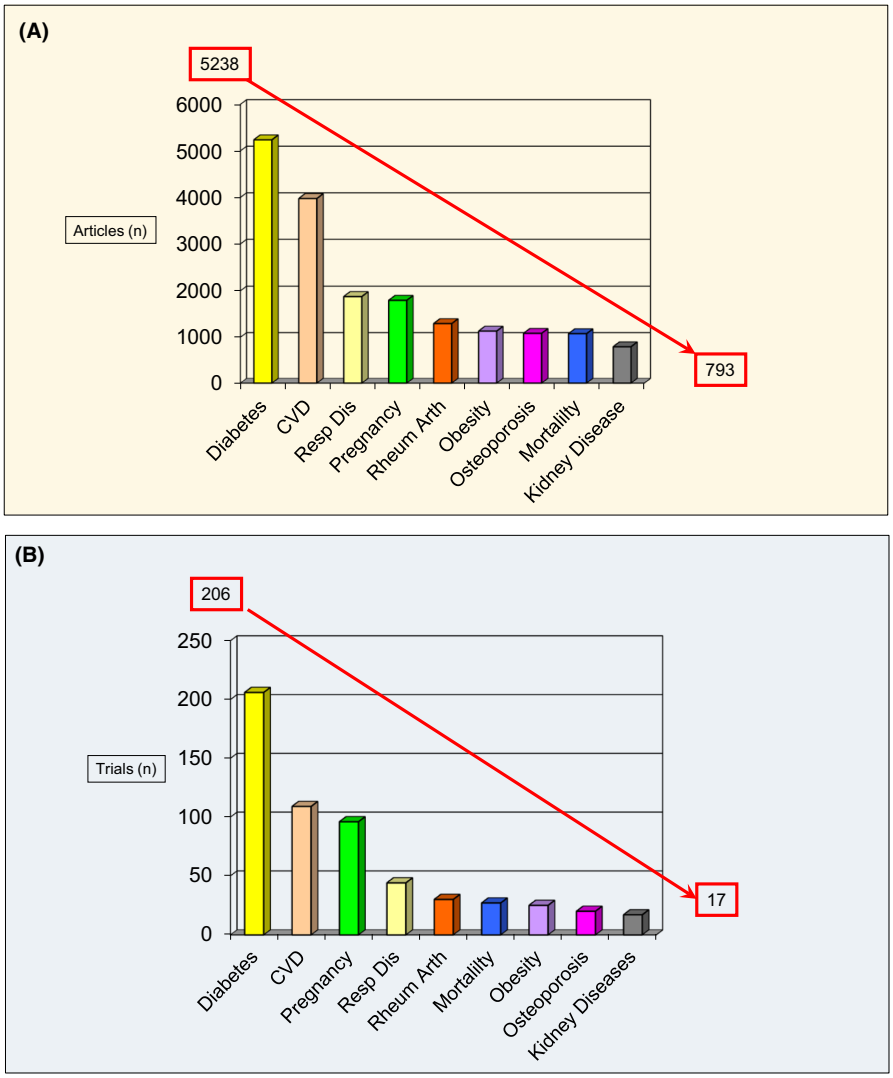

FIGURE 1 (A) Quantitative evaluation (number of articles) of the literature on the relationship between periodontitis and other diseases (source PubMed; without filter; September 13, 2023). (B) Qualitative evaluation (number of clinical trials) of the literature on the relationship between periodontitis and other diseases (source PubMed; filter: clinical trial; September 13, 2022).

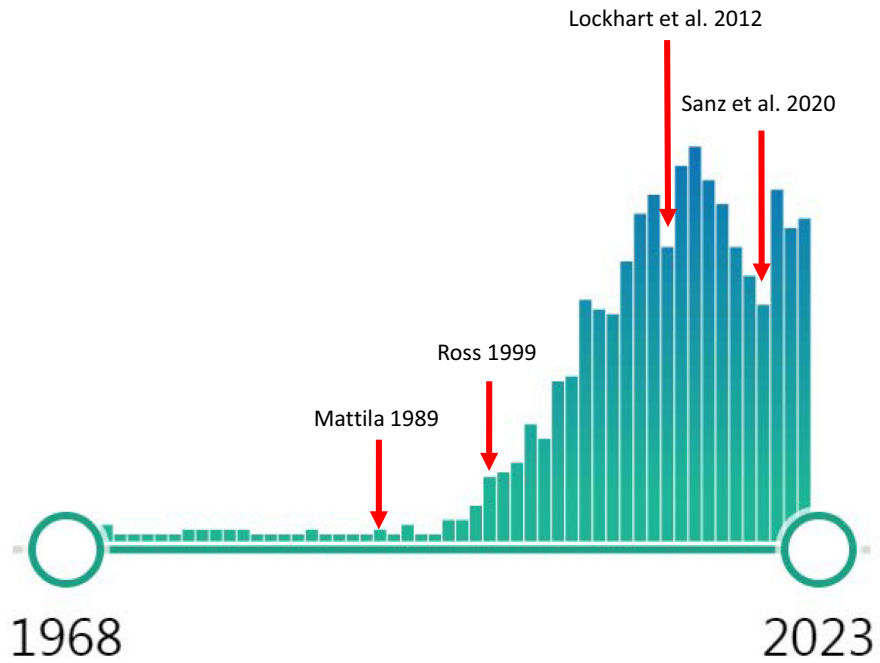

FIGURE 2 Number of studies per year from 1968 to 2023 retrieved without filter on PubMed using "periodontitis AND atherosclerotic cardiovascular disease" as general search terms (search on September 13, 2023). Red arrows indicate key articles that mark the overall history of the periodontal–cardiovascular relationship.

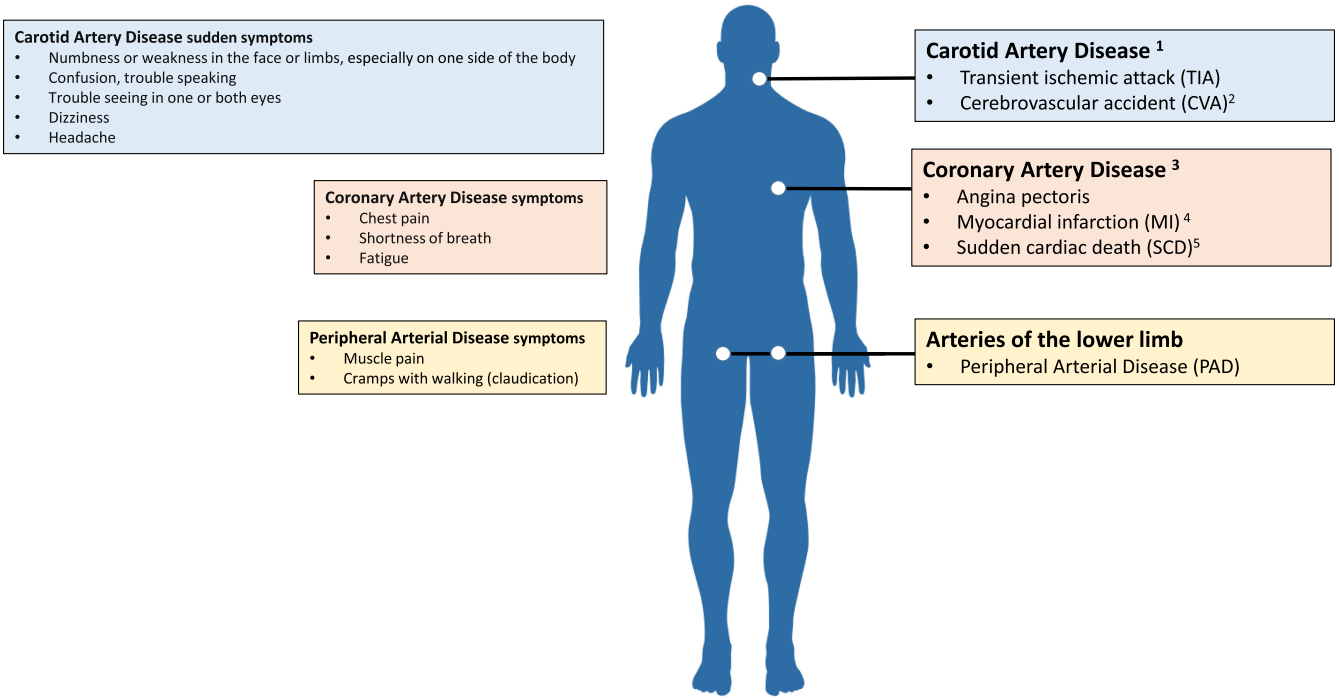

FIGURE 3 Atherosclerotic cardiovascular disease (ASCVD): common symptoms. *Synonyms*: [1]Carotid Artery Stenosis; [2]Stroke; [3]Coronary Heart Disease, Ischemic Heart Diseases; [4]Heart Attack; [5]Coronary Heart Disease death.

TABLE 1 Main differences between infective endocarditis and atherosclerosis.

	Infective Endocarditis	Atherosclerosis
Onset	**Sudden**, acute	**Slow**, silent disease
Cause	**Infection** (usually HACEK[a] organisms or less commonly fungi)	**Inflammation**
Symptoms	**Flu-like** [fever: rectal temperature of 100.4 °F (38°C) or above, chills]	**Absent** or angina pectoris, transient ischemic attack (TIA), peripheral arterial occlusive disease (PAOD)
Prevalence/ incidence	Very **low**	Very **high**
Mortality	**High** (6-month mortality >30%, even with antibiotic treatment[a])	**Depends on the complications**. Can be high: myocardial infarction, stroke
Primary prevention	**Limitation of bacteremia**: good oral hygiene, systematic disinfection of wounds. Antibiotics in high-risk patients only.	**Healthy lifestyle**. Lipid-lowering agents in high-risk patients only.
Secondary prevention	**Antibiotics** with at-risk procedures, especially dental procedures	**Lipid-lowering agents** plus medications according to the complication

[a]HACEK organisms: ***H****aemophilus* spp., ***A****ggregatibacter actinomycetemcomitans*, ***C****ardiobacterium hominis*, ***E****ikenella corrodens*, and ***K****ingella kingae*.

1950s, infection was the watchword, and bacteria were the cause of most human diseases. Although the role of inflammation in the pathogenesis of ASCVD was mentioned quite early in the 1970s,[20] it was not until the late 1990s that it was seriously considered, opening the way to an increasing number of publications and a paradigm shift in thinking[21] (Figure 2).

In 1989, that is, 64 years after the focal infection theory, Kimmo Mattila published a seminal paper showing an association between dental health and acute myocardial infarction (AMI).[22] The article paved the way for a new field of research in dentistry and opened new avenues for the prevention of ASCVD. In addition, it concluded that "*...dental caries or periodontal disease, or both, are more common among patients with acute myocardial infarction than among controls*," which stimulated the medical community's interest toward the risk associated with oral inflammation.

Finally, in 2012, a scientific statement from the American Heart Association claims: "*Observational studies to date support an association between periodontal pocket depth and atherosclerotic vascular disease, independent of known confounders. They do not, however, support a causative relationship*".[23]

1.2 | Where are we now?

Today, it is clear that the main objective is no longer to simply cure diseases but also and above all, to prevent them. The key messages

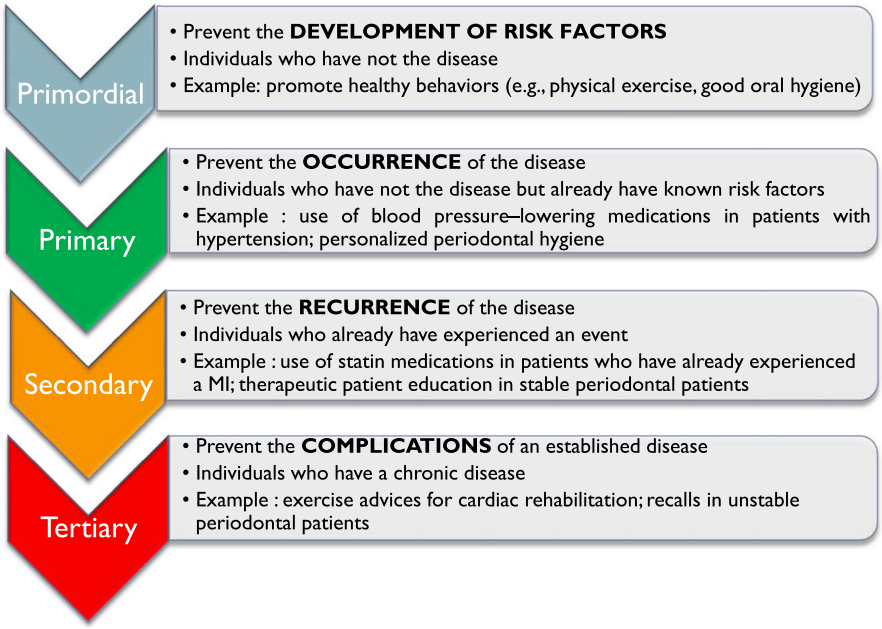

FIGURE 4 The different levels of prevention.

of the most recent guidelines of the European Society of Cardiology developed by the task force for cardiovascular disease prevention in clinical practice confirm the association between periodontitis and ASCVD.[13]

This raises two questions: (1) can prevention and/or treatment of oral diseases prevent other diseases, including atherosclerosis, which is of interest to a large segment of the population?; and (2) at what level of cardiovascular prevention can the prevention and/or treatment of oral diseases, in particular of periodontitis, have an impact (Figure 4)? Nowadays, it is not easy to answer these questions directly, mainly because of the methodological issues detailed below.

1.3 | Where do we go?

Regardless of the difficulties associated with research into periodontal systemic links, the independent association between periodontitis and ASCVD has been widely demonstrated. The research on this topic is highly relevant due to the potential implications in terms of ASCVD prevention. We know that we face two prevalent diseases, periodontitis and ASCVD. The diagnosis of periodontitis is easy to perform accurately. Leaving aside severe periodontitis (Stages III & IV) that may require complex and multidisciplinary therapies, the treatment of periodontal diseases is standardized, commonly performed by oral healthcare practitioners, and highly efficient in reducing the inflammation and the bacterial load in the patient's mouth.[24] Furthermore, the treatment of periodontitis is cost-effective.[25] The next step is to investigate the potential causality between the diseases and to tailor periodontal treatment to the cardiovascular condition(s). In the future, we should try to answer the question: what is the prognosis of ASCVD in periodontal patients receiving periodontal therapy compared to that of periodontal patients without periodontal therapy?

2 | THE EPIDEMIOLOGICAL LINK BETWEEN PERIODONTITIS AND ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

Epidemiologic studies have attempted to establish the association between periodontitis and ASCVD to answer the question "Is periodontitis (exposure) a risk factor for incident ASCVD (outcomes)?" This question is obviously relevant to both prevention and treatment. However, it directly implies causality. Thus, leaving aside the classical selection and publication bias, several methodological issues specific to the periodontal–ASCVD link must be considered to properly conduct and interpret epidemiological studies (Box 3).

2.1 | Methodological issues

2.1.1 | The study design

Because of the difficulties associated with interventional studies (such as randomized controlled trials, RCTs), clinical trials are scarce (Figure 1B). Consequently, observational studies (cross-sectional and cohort studies), mostly based on surrogate end points, today provide the best available evidence on the association between periodontitis and cardiovascular events at the population level. Thus, evaluating the consistency of the epidemiological evidence is of crucial importance.

BOX 3 Methodological issues when investigating the association between periodontitis and ASCVD.

- The study design
  - Observational
  - Experimental
- Heterogeneity of the indicators
- Case definition
  - Clinical diagnosis
  - Epidemiological diagnosis
- Control of confounders
  - Overadjustment
  - Risk of residual confounding
- The time factor
- Data quality
  - Data sources
  - Partial-mouth vs. full-mouth examination
  - Self-reported data
- Study population
  - Sample size
  - Age
  - Country and settings (representativeness)
  - Internal and external validity
- The collider bias
- The effect size

2.1.2 | Heterogeneity of the indicators

Exposure and outcome assessments vary significantly among the available studies. The oral evaluation of cardiometabolic risk is complex, and numerous oral and periodontal health variables, alone or in combination, have been connected to cardiovascular variables (Figure 5). Consequently, the quality of the evidence may change according to the choice of the connected variable, and no mediator[†] between the exposure (periodontitis) and the outcome (ASCVD) has been identified yet.

Periodontal disease evaluation has been based on the following three sets of criteria: (1) clinical evaluation, usually based on periodontal measurements (e.g., pocket depth and clinical attachment level) and oral hygiene indices,[1] number of missing teeth, and less commonly the number of masticatory units[26–29]; (2) radiographic evaluation; and (3) biological evaluation of oral fluids such as saliva and gingival fluid. All these variables were differentially associated with (1) cardiovascular events such as myocardial infarction (MI), cerebrovascular accident (CVA), and peripheral arterial disease (PAD); (2) cardiovascular risk factors; and (3) surrogate end points of ASCVD such as endothelial dysfunction, subclinical carotid or coronary disease, or systemic inflammation (e.g., hsCRP, IL-1, etc.).[30–32]

[†]The mechanism that transmits the effect of the exposure to the outcome.

Frequently, studies use proxies and surrogate markers for both exposure and outcome, which necessitates caution in the interpretation of results. Indeed, even if a surrogate marker, that is, a variable intended to substitute a clinical end point, correlates with the clinical end point, this does not guarantee the association. For example, assessing the relationship between periodontal pocket depth, as a surrogate measure to predict tooth loss, and endothelial dysfunction, as a surrogate measure to predict cardiovascular risk, does not guarantee that tooth loss predicts the occurrence of a cardiovascular event.

Among the set of criteria that can be used for the case definition of periodontitis, probing depth is certainly the best clinical parameter to achieve a clear relationship. Indeed, it corresponds to a clinical evaluation of the ongoing disease, which is not the case for the measurement of periodontal attachment loss or radiographic evaluation of bone loss, and it is consistent with the pathophysiological hypothesis associating periodontitis and ASCVD mainly through the inflammatory pathway.[33] Regarding the best end point for CVD, the incidence of clinical events such as MI, CVA, or PAD is obviously the most meaningful.

2.1.3 | The case definition

Comparability between studies is limited by the case definition used. Changing the case definition critically affects the data collected and the analysis of their combination. Many studies prior to the 2000s reported different classifications, making the comparison of their results difficult. Ideally, a case definition should be both specific and sensitive, which corresponds to an AUC ≥0.8. As a general rule, a case definition for a clinical diagnosis should be highly sensitive because the goal is to set the most accurate treatment, whereas a case definition in epidemiology should be highly specific because the goal is to set the most accurate prevalence. The introduction in 2018 of a new classification for periodontal diseases and conditions,[34] promoted by the EFP and AAP, should facilitate future clinical intergroup comparisons since it should be adopted worldwide. However, in epidemiology, the CDC/AAP classification for periodontitis (i.e., mild, moderate, and severe forms) remains the most commonly used[35] and still represents the global standard for periodontitis surveillance.[36,37]

2.1.4 | Control of confounders

Another potential pitfall frequently encountered in epidemiological studies is the control of confounders, both in the type of study design and in the statistical analyses performed. Most of the time, regression models and multivariable analyses are performed to take into account the known confounders in the association between periodontal diseases and ASCVD (e.g., age, sex, smoking, BMI, education, hypertension, and type-2 diabetes). Still, there is the potential risk of residual confounding (not controlled in the statistical analyses) as well as overadjustment.

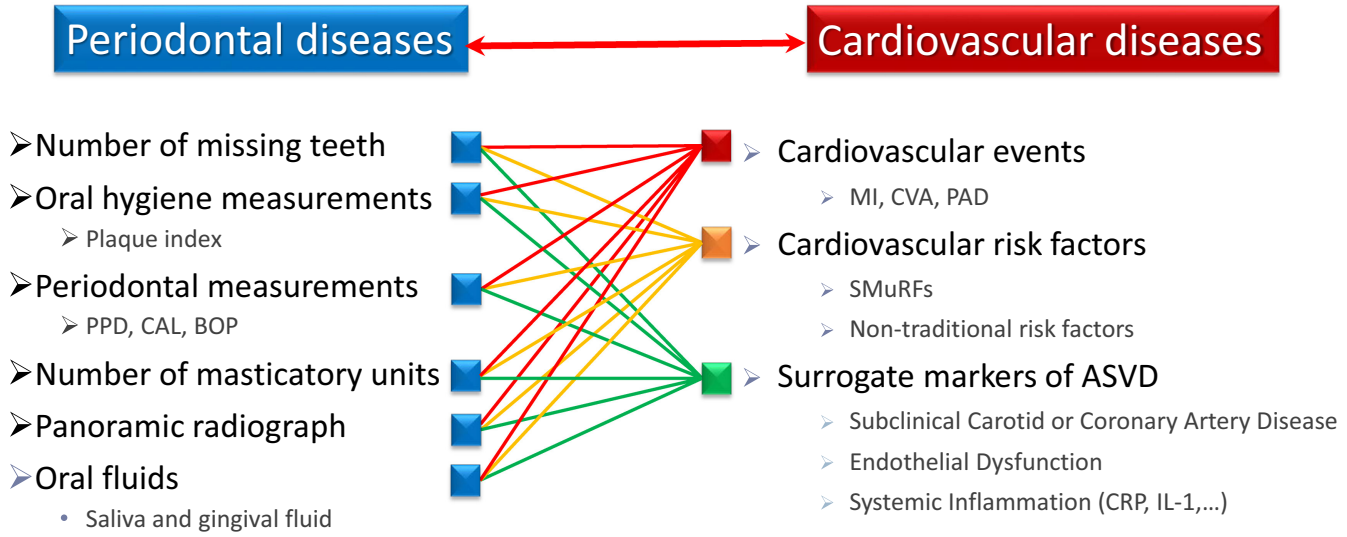

FIGURE 5 Periodontal clinical parameters related to cardiometabolic risk assessment. Abbreviations: CRP, C reactive protein; CVA, cerebrovascular accident; IL, Intetrleukin; MI, myocardial infarction; PAD, peripheral arterial disease; SMuRFs, standard modifiable cardiovascular risk factors.

2.1.5 | The time factor

Atheromatous plaque formation may start before the age of 10. Results from the Bogalusa Heart Study (USA), a long-term follow-up study from birth to the age of 38, demonstrated that ASCVD (coronary heart disease in particular) begins in childhood.[38] Thus, it is difficult to set a temporal relationship between a preventative measure and the occurrence of a cardiac event. Furthermore, one cannot discard the hypothesis of reverse causality. Indeed, the dysregulation of the immune system in the background of ASCVD could have an impact on susceptibility to periodontitis.[39]

2.1.6 | Data quality

Data quality and reliability are important in interpreting the results. Administrative clinical data and/or health insurance databases have been explored to document the association between periodontitis and ASCVD. These data sources are typically extracted from archived public health records, e-cohorts, or national databases, with the advantage of being gathered from large populations. However, some data are clinically recorded, sometimes using a partial-mouth examination protocol, which underestimates the number/severity of the cases, others may be self-reported. Self-reported data are more prone to reporting bias, whereas clinical data may be poorly recorded at the population level.

2.1.7 | The study population

Although statistical power is strictly depended on the sample size, the reader must keep in mind that good-quality data do not depend exclusively on the size of the sample. Larger sample sizes may provide more insightful information, a lower margin of error, and more accurate models, but the quality of the evidence is dependent on the use of appropriate sample selection techniques, the reliability and reproducibility of outcome assessment, and the sample frame and context in which data are collected. Furthermore, age is an important characteristic of the population when dealing with the relationship between periodontitis and ASCVD.

Most studies indicate an age-dependent association.[40,41] In general, in men older than 60 years (the exact age depends on the reference study), no association is found between periodontitis and the incidence of cardiovascular events. This may be due to confounding effects of the traditional risk factors for ASCVD, which outweigh the potential impact of periodontitis, particularly in the elderly.

The representativeness of the sample, the external validity of the results, as well as the comparability between different countries, according to their cultural and medical systems (e.g., insurance companies), must be taken into account. Most of the studies have been conducted in industrialized countries including individuals with insurance coverage, whereas socioeconomic factors are very much involved in the development of cardiovascular and periodontal diseases.[11,36,42]

2.1.8 | The collider bias

The role of mediators in the association between periodontitis and ASCVD is under investigation and should also be considered. To date, one cannot discard the proposal that periodontitis and CVD have a common effect on one or multiple colliders.[‡] In other

[‡]A collider is a variable independently caused by the exposure and the outcome. A collider bias is a distortion that modifies an association between an exposure and outcome, caused by attempts to control for a common effect of the exposure and outcome (https://catalogofbias.org/biases/collider-bias/)

words, a collider bias or an adjustment on mediators is not excluded. However, the fact that ASCVD and periodontitis share similar risk factors (such as diabetes, smoking, obesity, stress, low socioeconomic status, and low physical activity) and have common genetic pleiotropy[43] and health determinants (such as socioeconomic factors,[44-46] nutrition,[26] high diastolic blood pressure,[47] and body silhouette trajectory clusters [Saade Y et al. unpublished data]) makes the "common soil" hypothesis a relevant concept.[48] This concept is developed further in the present article. If we ever had evidence that periodontitis precedes the ASCVD event, which is still lacking, then one could hypothesize that periodontitis is a predictor of ASCVD.

2.1.9 | The effect size

Concerning the observed effect size, this is difficult to interpret due to the heterogeneous adjustments performed and the specificity of the populations investigated. In general, the strength of the association between periodontitis and ASCVD is small to moderate, but this can have a relevant clinical impact especially if targeted by potentially preventive actions (i.e., treating periodontitis to lower the risk of ASCVD and AH). Further studies on primary prevention interventions are awaited to elucidate the role of periodontitis on cardiovascular health.

However, nowadays, the independent association between periodontitis and ASCVD is no longer disputed.

2.2 | Update on epidemiological studies investigating the association between periodontitis and ASCVD

In 2019, for the joint EFP and WHF workshop, Herrera et al[4] updated the systematic review of Dietrich et al. including 11 additional studies published between 2012 and 2018. The authors' conclusions were confirmatory.[1,4] Continuing along this line, we have therefore updated the literature search limiting the evaluation and selection to epidemiological studies published since 2018. To update the literature review on ASCVD, we used the same terms (keywords and MeSH terms) as the previous reviews.[1,4] We added the types of epidemiological studies (cross-sectional, case–control, and cohort) to the search, and we limited the publication date between 2018 and 2022. Only studies considering adult patients (≥19 years) were selected (Table S1). Thus, 135 records were retrieved, and after screening on title and abstract first, and full-text then, 10 articles were finally included.

To explore the association between periodontitis and ASCVD, we tried to answer the following questions:

- Is there an association between periodontitis and first cardiovascular events due to ASCVD such as transient ischemic attack (TIA), cerebrovascular accident (CVA), angina pectoris, myocardial infarction (MI), sudden cardiac death (SCD), and peripheral arterial disease (PAD)?
- Is there an association between periodontitis and secondary cardiovascular events?

The characteristics of the studies included are summarized in Table 2. Data recorded from databases of South Korea (4 studies), Northern Europe (2 studies), North America (2 studies), India (1 study), and Asia (1 country) confirmed that periodontitis is associated with prevalent ASCVD. However, the prospective cohort study of Gao et al. ($n = 4591$)[49] and the cross-sectional study of Dain et al. ($n = 1286$),[50] failed to show a significant relationship between periodontitis and coronary heart disease (CHD). Similarly, the study of Beck et al[51] ($n = 6300$) failed to show a significant association between CDC/AAP case definition of periodontitis and incident CHD. The cross-sectional analysis of Wining et al[41] confirmed the association between periodontitis and prevalent MI ($n = 1274$) but failed to show an association between periodontitis and incident MI in men ($n = 1137$). Taken together, these pertinent studies published since the last systematic review on periodontitis and ASCVD indicate that there are substantial differences according to the definition used for periodontitis,[51] the severity of disease,[52,53] the patient's demographics (i.e., sex),[52] and the method of data collection.[53]

The level of evidence of the selected observational studies is rather low, including one case–control study,[54] and two prospective cohort studies.[49,51] Several methodological limitations in the study design and/or reporting are observed (e.g., unclear case definitions, partial-mouth examination of the periodontal status, lack of details on data recording, and use of raw insurance data), and these call for caution in the interpretation of the results. Overall, the more recent studies on the epidemiological association between periodontitis and ASCVD confirmed the previous findings with the same limitations and without providing new insights on these links. To answer the above-mentioned questions, there is evidence to support a significant association between periodontitis and ASCVD events, although data on incident ASCVD cases (first event and recurrent event) are still limited.

2.3 | Epidemiological studies investigating the association between periodontitis and arterial hypertension

Over the years, several studies suggested an association between periodontal diseases and AH, with the potential involvement of periodontitis as a risk factor for AH.[55,56] In fact, as periodontitis contributes to low-grade systemic inflammation, it might contribute to endothelial dysfunction and therefore impaired vasodilation responses that ultimately lead to increased blood pressure.[57] Furthermore, recent evidence suggested that periodontitis may cause immune-mediated blood pressure elevation associated with endothelial dysfunction in a dose-dependent manner,[58] with a

TABLE 2 Update on epidemiological studies investigating the association between periodontitis and ASCVD (May 24, 2023).

Publication/ Country	Database	Study design	Number of patients analyzed	Mean age at baseline	Study period or duration
Beck et al. 2020 USA	ARIC	Prospective cohort	6300	62.3 years	16.7 (SD: 5.5) years
Byon et al. 2020 South Korea	National Health Insurance Service—National Sample Cohort 2.0 (NHIS-NSC2)	Retrospective matched cohort	104 850 • 52 425 with diagnosis of periodontitis • 52 425 without diagnosis of periodontitis	NR • ≥ 20 years	January 2002 to December 2015.
Byun et al. 2020 South Korea	Korean Genome and Epidemiology Study Health Examinee (KoGES HEXA)	Cross-sectional	135 277 • 9973 reporting periodontitis • 125 304 not reporting periodontitis	• Reporting periodontitis: 54.8 (7.9) years • Not reporting periodontitis: 53.0 (8.3) years	2004–2016
Cho et al. 2020 South Korea	National Health Insurance Service–Health Screening Cohort (NHIS-HEALS)	Retrospective matched cohort	145 972 • 72 971 with diagnosis of periodontitis • 72 971 without diagnosis of periodontitis	• 54.9 (8.9) years with diagnosis of periodontitis • 55.1 (10.4) years without diagnosis of periodontitis	January 2003 to December 2014.
Cho et al. 2021 South Korea	National Health Insurance Service–National Health Screening Cohort (NHIS-HEALS)	Retrospective cohort	298 128 • 116 194 with severe periodontitis • 181 934 without severe periodontitis	• Severe periodontitis: 55.52 (9.00) y • Moderate Periodontitis: 53.12 (8.35) y • Healthy: 54.65 (9.68) y	• Baseline: 2002 to 2005 • Follow-up: 2006 to 2015
Dain et al. 2021 South India	CSI Kerala CRP Study	Cross-sectional	1286 • 725 from rural area • 560 from urban area	NR • ≥45 years	January to June 2011.
Gao et al. 2021 China	Beijing health management cohort (BHMC)	Prospective cohort study	4591 • 1268 with diagnosis of periodontitis	53.9 (11) years	2014 to 2019
Gustafsson et al. 2020 Sweden	PAROKRANK study	Case–control	1392 • 696 cases with first MI • 696 controls without history of MI	NR • <75 years	May 2010 to February 2014.

Periodontal variable recorded	Definition of periodontitis	Cardiovascular variable(s) recorded (outcome)	Strength of the association after adjustment	Authors' comments and main conclusions
Full-mouth, six sites examination • BOP • PD • GR • CAL • Plaque index	Periodontal Profile Class System (PPC) and CDC/AAP definition	Incident coronary heart disease (CHD)	• HR is 1.59 [1.13 to 2.23] for incident MI in the severe tooth loss (PPC stage VII) group • HR is 5.27 [1.80 to 15.4] for fatal CHD in the mild tooth loss/high gingival inflammation (PPC stage V) group • The CDC/AAP definition is not significantly associated with incident CHD.	• Severe subtypes of periodontal disease are at increased risk for incident CHD • Periodontal definition makes a difference in the results
NR	Korean Classification of Diseases, 7th revision (KCD-7) • Acute periodontitis • Chronic periodontitis • Periodontosis • Other periodontal diseases • Periodontal disease, unspecified	Korean Classification of Diseases, 7th revision (KCD-7) • Atherosclerosis • Cerebral atherosclerosis • Atherosclerotic cardiovascular disease, so described • Atherosclerotic heart disease	HR is 1.09 (95% CI: 1.05–1.13) for ASCVD in the periodontitis group	Periodontitis can increase the risk of ASCVD
Self-reported periodontitis	NR	Self-reported Stroke/Ischemic Heart Disease	• OR is 1.35 (95% CI: 1.16–1.57) for stroke in the periodontitis group • OR is 1.34 (95% CI: 1.22–1.48) ischemic heart disease in the periodontitis group	Periodontitis is associated with CVD
NR	Korean Classification of Diseases, 7th revision (KCD-7) • Acute periodontitis • Chronic periodontitis	Korean Classification of Diseases, 7th revision (KCD-7) • Peripheral arterial disease (PAD)	HR is 1.15 (95% CI: 1.07–1.23) for PAD in the periodontitis group	The incidence of PAD is increased in patients with periodontitis
NR	Korean Classification of Diseases, 7th revision (KCD-7) • Acute periodontitis • Chronic periodontitis	• Acute myocardial infarction (AMI) • Stroke • Nonfatal major adverse cardiovascular events (MACE) (composite of AMI and Stroke)	Compared to nonsevere group • HR is 1.11 (95% CI: 1.02–1.20) for AMI in the severe periodontitis group • HR is 1.035 (CI: 1.01–1.07) for stroke in the severe periodontitis group • HR is 1.047 (95% CI: 1.01–1.07) for nonfatal MACE in the severe periodontitis group	• The association with AMI and MACE is highly modified in females and adults aged 40 to 59 years • Severe periodontitis is causally associated with new events of AMI and stroke
Partial-mouth, four sites examination • PD • CAL	Modification of the Ramfjord periodontal disease index • Partial mouth: 6 teeth • Score 0 to 3: gingivitis • Score 4 to 6: periodontitis	Coronary Heart Disease (CHD)	OR is 1.54 (95% CI: 0.44–5.4) for CHD in both rural and urban areas	Periodontitis was not found to be an independent, significant risk factor for CHD
• PD • BOP • CAL • Bone level	Pocket depth > 3 mm + BOP + CAL + Bone resorption	Coronary Heart Disease (CHD)	RR is 1.37 (95% CI: 0.96–1.95) for CHD in the periodontitis group	Periodontitis was weakly associated with an increased risk of CHD
Full-mouth, four sites examination • Panoramic radiograph • PD • BOP	Clinical Periodontal Disease (CPD) index ≥2	• Calcified carotid artery atheromas on panoramic radiograph • Myocardial infarction (MI)	OR is 1.75 (95% CI: 1.11 to 2.74) for MI in the periodontitis group combined with calcified carotid artery atheromas	Periodontitis associated with calcified carotid artery atheroma increases the risk of MI compared to either condition alone

(Continues)

TABLE 2 (Continued)

Publication/ Country	Database	Study design	Number of patients analyzed	Mean age at baseline	Study period or duration
Ngamdu et al. 2022 USA	National Health and Nutrition Examination Survey (NHANES)	Cross-sectional	2830	51.5 (13.6) ≥ 30 years	2013 to 2014
Winning et al. 2020 Northern Ireland	PRIME study (prospective epidemiological study of myocardial infarction)	Cross-sectional analysis of a longitudinal cohort	• Prevalence: 1274 men • Incidence: 1137 men	63.7 (3.0) • Range: 58–72	• Recruitment 1991–1994 • Periodontal examination 2001–2003

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; CHD, coronary heart disease; GR, gingival recession; MI, myocardial infraction; PD, probing depth.

proportional relationship between the severity of periodontitis and the increase in systolic blood pressure and left ventricular mass in patients with hypertension.[59,60] While using surrogate measures for periodontitis, a significant association was also found for poor oral hygiene, high gingival inflammation, and tooth loss with AH.[61–64]

Previous cross-sectional studies, which essentially explored the magnitude of the association between periodontal diseases and AH, reported odds ratios ranging between 1.15 and 1.67 for periodontal patients to have AH.[55,56] The strength of this association varies between the studies, mainly due to methodological issues described above. For instance, age is a key factor when assessing the relationship between periodontitis and AH.[60,65–67] In the study by Darnaud et al,[60] which included 102 330 participants, a significant association between the oral health variables, namely missing teeth (>10 teeth), high levels of dental plaque, and high gingival inflammation, and AH was found only among subjects <65 years of age.

In a cohort of 572 adult industrial workers in Japan, Morita et al[67] observed that exposure to periodontitis was significantly associated with cardiometabolic risk factors, such as obesity, dyslipidemia, hyperglycemia, and AH, during a 9-year follow-up period. In particular, participants with periodontal pockets for ≥6 years (untreated periodontitis) had a 2.2-fold greater risk of AH compared to participants without periodontitis. Data from the South Korean National Health Insurance Service–Health Examinee Cohort (2002–2013), enrolling 200 026 individuals with periodontitis and 154 824 individuals with a healthy oral status, showed a significant association between periodontitis and AH, after adjustment for sex, age, household income, insurance status, area of residence, health status, and smoking.[68] The most recent systematic review and meta-analysis on the topic, based on 81 studies published up to December 2018 (of which 46 were used for pooled data analyses), concluded that patients with moderate-to-severe periodontitis have greater (20%–50%) odds of having AH when compared to patients without periodontitis. In addition, data suggested a positive linear association between the severity of periodontitis and the likelihood of having AH.[56]

Thus, we updated the literature search to provide a critical appraisal of the most recent studies (published since 2018) assessing the association between periodontitis and AH at the epidemiological level. As for ASCVD, periodontitis was the exposure and AH the outcome and should be assessed in cross-sectional or longitudinal studies. The literature search was conducted using the same keywords and MeSH terms as in the previous review in Munoz Aguilera et al,[56] while adding the type of epidemiological studies and limiting the publication date to 2018–2022 (Table S2). Thus, 107 articles on periodontitis and hypertension were initially found, of which 13 were selected and summarized (Table 3).

To explore the association between periodontitis and AH, we tried to answer the following questions:

- Is periodontitis a risk factor for AH?
- Does the severity of periodontitis influence the degree of AH and the related risk of cardiovascular diseases/events?

Overall, the literature is consistent and supports a significant association between periodontitis and prevalent/incident AH.

Zhao et al,[69] in a retrospective cross-sectional study, assessed the impact of periodontitis on the risk of AH in a Chinese population. The

Periodontal variable recorded	Definition of periodontitis	Cardiovascular variable(s) recorded (outcome)	Strength of the association after adjustment	Authors' comments and main conclusions
Home interview, followed by a standardized assessment at a mobile examination center • CAL	2017 World Workshop Classification of Periodontal and Peri-implant Diseases and Conditions (stages I to IV periodontitis)	Composite of self-reported stroke/coronary heart disease	• OR is 3.59 (95% CI: 1.12 to 11.54) for stages III/IV patients compared with stage I for CVD occurrence • OR is nonsignificant (2.17 [95% CI 0.98 to 4.79]) for participants reporting fair/poor gum health compared with those who reported excellent/very good gum health.	• Periodontal disease severity is associated with cardiovascular risk • Periodontal examinations are more reliable than self-reported measures
Full-mouth, six sites examination • PD • CAL	CDC/AAP definition	Myocardial Infarction (MI)	• Prevalence: OR is 2.15 (95% CI 1.15–4.02) for CHD events in men with highest mean CAL (Q4) compared with men with the lowest CAL (Q1). • Incidence: HR is 1.36 (95% CI 0.81–2.29) for CHD events in men with highest mean CAL (Q4) compared with men with the lowest CAL (Q1).	• Periodontitis is associated with prevalent CHD at baseline • Periodontitis is not associated with incident CHD

study included 3952 people aged 30–69 (including 2761 patients with AH). AH risk was associated with periodontal disease after adjustments (OR = 1.34; 95% CI: 1.14–1.58; $p < 0.0001$). Moreover, in a subgroup analysis, the risk of developing AH was highest in patients with periodontitis and up to 40 years of age [OR 1.694 (95% CI 1.196–2.398)].

Pietropaoli et al,[70] analyzed data from NHANES III cohort, and based on a sample of 8614 individuals aged 30 years or more, they found a significant association among the periodontal inflamed surface area (PISA), bleeding on probing (BOP), and the risk of AH. Specifically, severe PISA (≥37.6 mm^2) was associated with 43% higher odds of high/uncontrolled blood pressure, and BOP+ with 32% higher risk. Consistently, in another cross-sectional propensity score-matched analysis of a subset population from the same database (NHANES III), gingival bleeding was found to be independently associated with higher mean systolic blood pressure (by 2.6 mmHg), and with about 40% greater odds of high/uncontrolled blood pressure compared with nonbleeding. The authors concluded that gingivitis and unstable periodontitis were consistently associated with higher mean systolic blood pressure and greater odds of AH.[71]

Munoz-Aguilera et al[72] also analyzed data from representative population-based surveys in the USA (NHANES; $n = 3460$) and Korea (KNHANES; $n = 4539$) and observed a consistent and significant increased risk of AH in individuals with periodontitis in both populations (OR ranging between 1.2 and 1.3). These associations were independent of age, gender, BMI, education level, smoking, alcohol consumption, creatinine, physical activity, and presence of other comorbidities and confirmed in participants not taking antihypertensive medications.

In another cross-sectional study on a representative sample of the general Portuguese population ($n = 1057$), Machado et al[73] showed that the risk of AH depended on and was proportional to the stage of periodontitis (I, II, and III stages) varying from 1.72, 2.60, to 2.20, respectively. These significant associations were confirmed in different statistical models, but when the analysis was adjusted for age, the statistical significance was lost. The authors constructed a mediation model for age in the relationship between periodontitis and AH, which confirmed that the effect of periodontitis on blood pressure is strongly confounded by age.

Concerning longitudinal cohort studies, the study by Carra et al[47] based on the French e-cohort NutriNet-Santé ($n = 32\,285$) showed that self-reported periodontitis (assessed by calculating the mPESS score on the French validated version of the CDC/AAP questionnaire for periodontal diseases[74]) at baseline was an independent predictor of incident AH over an 8-year follow-up. Similarly, a significant association was found for the condition of having missing teeth that were not replaced with dental prostheses and incident AH. This study also showed that visiting the dentist regularly on an annual basis was associated with a 12% lower risk of developing AH compared to not visiting the dentist. Although limited by the self-reported assessment of both exposure and outcome, this study supports the causal link between periodontitis and AH as the temporal relationship was respected. These results were confirmed by Hwang et al,[75] who assessed the association between periodontitis and incident AH in a population-based sample of 104 349 participants from the National Health Insurance System-Health Screening (NHIS-HEALS) cohort. Over a mean follow-up of 9.6 years, a total of 52 855 (50.7%) patients had incident AH, with a greater incidence in participants with periodontitis (HR = 1.02; 95% CI: 1.00–1.04). The authors also reported that the number of missing teeth was positively associated with incident AH, and the high missing teeth group

TABLE 3 Update on epidemiological studies investigating the association between periodontitis and arterial hypertension (May 24, 2023).

Publication/ Country	Database	Study design	N	Mean age at baseline	Study period or duration	Periodontal variable(s) recorded
Hwang et al. J Periodontal 2022 KOREA	National Health Insurance System–Health Screening (NHIS-HEALS) cohort	Prospective cohort study	104 349	51.1 years (range 40–79) at baseline	9.6 years	Clinical examination
Munoz Aguilera et al. Hypertension 2021 UK	Participants recruited at the University College London Eastman Dental Institute	Nested Case–Control Study	500	Median age: 35 years	2001–2018	Full-mouth periodontal examination carried out by calibrated examiners
Carra et al. J Hypertension 2021 FRANCE	NutriNet-Santé e-cohort	Prospective e-cohort	32 285	45.79 (SD: 13.87) years	8 years (baseline April 2012; follow-up December 2019)	Self-reported
Pietropaoli et al. J Clin Periodontol 2020 USA	NHANES III	Cross-sectional study	8614	≥ 30 years	1988 to 1994	Periodontal inflamed surface area (PISA) calculated on clinical parameters recorded during the periodontal examination (PD, CAL, REC, BOP)
Pietropaoli et al. J Hypertension 2020 USA	NHANES III	Survey-based propensity score matching analysis (cross-sectional)	5396	≥ 30 years	1988 to 1994	Periodontal examination (PD, CAL, REC, BOP)
Chiu et al. Australian Dent Journal 2020 Hong Kong	Convenient sample of adult patients attending a university teaching hospital	Cross-sectional study	204	52.4 years	2010–2011	Periodontal examination carried out by calibrated examiners (PD, CAL, REC, BOP, PI)

Definition of periodontal status	Hypertension/Blood pressure assessment	Strength of the association after adjustment	Main conclusions
Insurance codes	Patients' clinical records. Incidence of AH was determined 1 year after the baseline. AH was diagnosed using ICD-10 code I10 in the medical records or the occurrence of high blood pressure (SBP ≥140 mmHg or DBP ≥90 mmHg)	• Periodontitis: (HR: 1.02; 95% CI: 1.00–1.04) • Number of missing teeth (for ≥15 groups, HR: 1.40; 95% CI: 1.29–1.52), • Dental scaling (HR: 0.93; 95% CI: 0.91–0.95), • Toothbrushing frequency (for ≥3 group, HR: 0.85; 95% CI: 0.83–0.88) significantly associated with incident AH. Periodontitis was associated with incident AH (HR: 1.04; 95% CI: 1.02–1.06) in the middle-aged group (40–64 years), the effect was not significant in the older group (≥65 years)	Periodontitis is associated with incident AH
Periodontitis case definition was of generalized severe/stage III/IV periodontitis	Office BP measurements were obtained following a standardized protocol (average of three measurements). Diagnostic US thresholds: SBP ≥130 mm Hg or DBP ≥80 mm Hg and European values: SBP ≥140 mm Hg or DBP ≥90 mm Hg	• A 14% of cases presented with SBP≥140 mm Hg versus 7% of the controls • >43% of the cases presented with DBP≥80 mm Hg versus 34% of the controls ($p = 0.035$). • 15.6% of the whole study participants presented with values of SBP/DBP in the range of AH (European definition): 17.2% of the cases and 14% of the controls ($p = 0.324$) • Based on the American definition of AH: almost 50% of cases and 41.6% of controls ($p = 0.073$)	Association between case definition of periodontitis (categorical) and higher mean SBP after adjusting for common risk factors. No significant association was found with SBP≥130 mm Hg, DBP≥90 mm Hg, or AH definition according to European or American guidelines.
Validated French version of the CDC/AAP questionnaire to identify participants at risk of severe periodontitis (mPESS ≥ 5)	Incident AH assessed as self-report of first-time diagnosis of AH and/or use of antihypertensive therapy	Participants with mPESS ≥ 5 showed a significantly greater occurrence of AH during the 8-year follow-up period (HR: 1.84; 95% CI: 1.66–2.03)	Self-reported severe periodontitis (mPESS ≥ 5) at baseline is an independent predictor of AH development during an 8-year follow-up
Severe PISA (≥ 37.6 mm2)	Average of three measurements of BP by trained and calibrated personnel using a standard mercury sphygmomanometer	Risk of AH: • OR: 1.43 (95% CI: 1.17–1.74) for severe PISA and • OR: 1.32 (95% CI: 1.08–1.60) for BOP	Patients with severe PISA and BOP appear at higher risk of high/uncontrolled BP
Gingival inflammation (BOP+) as proxy for gingivitis and unstable periodontitis	Average of three measurements of BP by trained and calibrated personnel using a standard mercury sphygmomanometer.	Gingival bleeding was independently associated with +2.6 mmHg in SBP compared with no bleeding. Unstable periodontitis (OR:1.65; 95% CI:2.14–1.82) and gingivitis (OR: 1.49; 95% CI: 1.22–1.82) were associated with high/uncontrolled BP	Gingival bleeding is independently associated with higher mean SBP (by 2.6 mmHg), and with about 40% greater odds of high/uncontrolled BP compared with nonbleeding. Gingivitis and unstable periodontitis were consistently associated with higher mean SBP and greater odds of high/uncontrolled BP
AAP/CDC case definition	Average of two measurements of BP using a standard mercury sphygmomanometer.	Severe periodontitis was significantly and independently associated with high BP	Periodontitis severity was found to be associated with essential AH

(Continues)

TABLE 3 (Continued)

Publication/ Country	Database	Study design	N	Mean age at baseline	Study period or duration	Periodontal variable(s) recorded
Machado et al. J Clin Med 2020 PORTUGAL	Periodontal Health in Almada-Seixal (SoPHiAS)	Representative cohort	1057	18–95 years	December 2018 and April 2019	Full-mouth periodontal examination performed by two trained and calibrated examiners (PD, PISA, PI, BOP, CAL)
Munoz Aguilera et al. J Internal Med 2020 USA	National Health and Nutrition Examination Survey (NHANES) + Korean National Health And Nutrition Examination Survey (KNHANES)	Cross-sectional study	3460 + 4539	51 and 45.9 years	2009–2010 for the US population-based surveys and 2015 for the Korean survey	In the NHANES, a full-mouth periodontal assessment, whereas in the KNHANES study, the community periodontal index (CPI) was used
Teixeira et al. Braz Oral Res 2020 BRAZIL	Advento study (Analysis of Diet and Lifestyle for Cardiovascular Prevention in Seventh-Day Adventists)	Cross-sectional study	420	35 to 74 years Mean age 53.5 ± 10.5 years	NR	Periodontal examination performed by four trained and calibrated examiners (PD, CAL, BOP)
Lee et al. Medicina 2020 South Korea	National Health Insurance Service—Elderly Cohort	Cross-sectional study	558 147	≥60 years	2002–2015	National Health Insurance Program codes
Furata et al. J Oral Sci 2019 JAPAN	Patients regularly visiting private dental clinics	Nationwide cross-sectional survey	999	≥40 years	NR	Clinical examination
Gordon et al. Am J Hypert 2019	Women's Health Initiative—Observational Study	Prospective cohort study	36 692	All postmenopausal women, with a mean age of 67.1 (7.0) years	Initial periodontal assessment (1998–2003) through 2015. Mean follow-up 8.3 years	History of periodontal disease diagnosis and/or edentulism. Periodontal disease was assessed on the year-5 questionnaire as "Has a dentist or dental hygienist ever told you that you had periodontal or gum disease?". Edentulism was assessed using the question "Have you lost ALL your permanent teeth, both upper and lower?".

Definition of periodontal status	Hypertension/Blood pressure assessment	Strength of the association after adjustment	Main conclusions
EFP/AAP 2018 classification for gingivitis and periodontitis cases (stages)	One-single measure with automated sphygmomanometer device	• Significant association between high BP and periodontitis (O: 2.31; 95% CI: 1.75–3.04, $p<0.001$). • In the fully adjusted model, the association was no longer significant (OR: 1.36; 95% CI: 0.84–2.18 for mild periodontitis; OR: 1.41; 95% CI: 0.92–2.15 for moderate periodontitis; and OR: 1.04; 95% CI: 0.69–1.55 for severe periodontitis). • The % of sites with PD ≥ 6 mm and BoP showed a positive significant association with increased SBP and DBP	The results confirm an association between high BP and periodontitis, which, however, is confounded by the age factor
For the NHANES: Continuous aggregate dental variables (number and % of sites) were then created to indicate (a) the extent of periodontal lesions with PD ≥4 mm, ≥5 mm, ≥6 mm, and (b) the extent of CAL of ≥3 mm, ≥4 mm, ≥5 mm, and ≥6 mm. For the KNHANES: CPI 3 or 4 defined periodontitis	Sitting BP measured using a standardized protocol. AH was defined as values of SBP ≥140 mmHg or DBP ≥90 mmHg or the use of antihypertensive medication(s)	Participants with periodontitis were more likely to have AH (NHANES: OR = 1.3, 95% CI: 1.0–1.6, $p=0.025$; KNHANES: OR = 1.2, 95% CI: 1.0–1.4, $p=0.041$) and actual SBP≥140 mmHg (NHANES: OR = 1.6, 95% CI: 1.1–2.3, $p<0.001$; KNHANES: OR = 1.3, 95% CI: 1.0–1.6, $p<0.031$) than those without the disease. These associations were independent of age, gender, BMI, education level, smoking, alcohol consumption, creatinine, physical activity, and presence of other comorbidities and confirmed in participants not taking antihypertensive medications. Mediation analyses confirmed that CRP acted as a mediator in the association between periodontitis and AH in both populations	Periodontitis is closely linked to AH and systemic inflammation
Periodontitis was defined and classified on the Community Periodontal Index (CPI) scores 3 and 4	Mean of three measurements using a standard sphygmomanometer	Patients with periodontitis have significantly higher prevalence of AH in both age groups (<55 years: prevalence of 40%; and ≥ 55 years: prevalence of 46.6% compared to 21.4% and 38.1%, respectively, in the nonperiodontitis patient group)	Significant association between periodontitis and AH
National Health Insurance Program codes	National Health Insurance Program codes	Periodontal disease was significantly associated with AH (OR = 1.4; 95% CI: 1.38–1.42)	Periodontal disease was significantly associated with AH
Periodontitis defined as 2 or more teeth with a CAL ≥6 mm	Self-reported questionnaire	AH was associated with a larger number of teeth with a PD ≥5 mm (PRR 1.27, 95% CI: 1.02–1.58)	AH is associated with worse periodontal disease in periodontal patients who regularly visited private dental clinics
Self-reported	Self-reported questionnaire updated annually	Periodontal disease was not associated with an increased risk of AH in the multivariable-adjusted models (HR 0.99; 95% CI: 0.95–1.03). There was significant interaction between age and baseline SBP	Only edentulism was significantly associated with incident AH

(Continues)

TABLE 3 (Continued)

Publication/ Country	Database	Study design	N	Mean age at baseline	Study period or duration	Periodontal variable(s) recorded
Zhao et al. Frontiers in Physiology 2019 CHINA		Retrospective cross-sectional study	3952	30–68 years	2017	Community Periodontal Index of Treatment Needs (CPITN) according to the WHO guidelines

Abbreviations: AH, arterial hypertension; BOP, bleeding on probing; BP, blood pressure; CAL, clinical attachment loss; DBP, diastolic blood pressure; PD, pocket depth; PI, plaque index; REC, recession; SBP systolic blood pressure.

(≥15) had a higher AH risk than the no missing teeth group (HR: 1.40; 95% CI: 1.29–1.52). Dental scaling was negatively associated with the occurrence of AH (HR: 0.93; 95% CI: 0.91–0.95), and the risk of incident AH was lower in the higher-frequency toothbrushing group (≥3 vs. 0–1 times/day; HR: 0.85; 95% CI: 0.83–0.88). Importantly, stratified analyses by age group highlighted that the associations varied greatly with age, supporting previous studies,[60,72,73,75] that demonstrated age as the main confounder of this association.

Despite this, the literature overall is consistent in finding a significant epidemiological association between periodontitis and AH.[76]

3 | BIOLOGICAL PLAUSIBILITY

Periodontal bacteria, as well as their products, can access the bloodstream dynamically from the inner portion of the ulcerated periodontal pocket of patients affected by periodontitis. Being predominantly anaerobic, pathogenic oral bacteria must rapidly hide from the oxygenated compartment of the bloodstream. The presence of periodontal bacteria has been consistently reported in pathological tissues of patients affected by ASCVD. Because of their tropism for fibrin and other extracellular matrix molecules, periodontal bacteria can easily adhere at sites of arterial injury, throughout the cardiovascular system.

3.1 | Plausible dissemination pathways of periodontal pathogens toward cardiovascular lesions

The current paradigm postulates that periodontal pathogens reach atherosclerotic lesions via a "hematogenous spread." Indeed, the frequent episodes of gingival pocket ulceration associated with gingival bleeding allow the entry of the periodontal bacteria into the blood stream. This hypothesis is supported by the observation that gentle toothbrushing and even chewing result in a "perio-specific" transient bacteremia in patients with periodontitis[77] and more abundant bacteremia consistently follows periodontal procedures.[78]

The oral–gut axis may represent another possible dissemination pathway because salivary microbiota can impact the gut microbiota via the liters of saliva we swallow every day.[79] A striking similarity among the bacterial DNA of the human oral, gut, and atherosclerotic plaques has been reported.[80] Of note, the translocation of the gut microflora into the bloodstream is favored by malnutrition,[81] which is both a cause and a consequence of periodontitis.[82] The frequency of pathogenic taxa in the salivary microbiota is reduced by periodontal treatment,[83,84] suggesting that oral health care can consistently limit the oral–gut dissemination route of periodontal pathogens.

3.2 | Pathophysiology: Evidence for pathogenicity of periodontal pathogens compared to other potential infectious agents

Periodontal pathogens can exert a deleterious role in the pathogenesis and outcomes of ASCVD by several mechanisms, as suggested by in vitro and in vivo experimental studies.

A myriad of different bacteria colonize the subgingival niche but only a small proportion of bacteria are consistently associated with the pathological inflammation that defines periodontitis. Among them, *Porphyromonas gingivalis (Pg)*, an obligate asaccharolytic gram-negative anaerobic bacterium, is most frequently found in periodontal pockets[85] as well as in atherosclerotic plaques.[86,87] The presence of *Pg* at sites of vascular lesions enhances and alters the local immune response driving several of the pathogenic sequelae involved in atherosclerosis.[88] The prevalence of *Pg* in diseased tissue is most likely explained by its ability to circumvent the immune response of the host.

Pg can evade the immune surveillance of monocytes, by accessing the cells via complement receptor 3 and TLR2,[89] while rendering these innate immune cells less responsive.[90] Yet, the presence of *Pg* enhances systemic inflammation by reducing the regulatory T cell pool[91] and promoting the local release of pro-inflammatory cytokines,[92] eventually aggravating tissue damage at the site of vascular lesions. Although *Pg* is the most studied microbial target in periodontitis and ASCVD, other members of the periodontal microbiota, such as *Aggregatibacter actinomycetemcomitans*,[93] *Tannerella forsythia*,[94] or *Treponema denticola*,[95] have also been shown to potentially link periodontitis and accelerated atherosclerosis in experimental murine models. Additionally, the pathogenic impact of periodontitis in ASCVD could be due to the immunological responses induced by the periodontal dysbiosis, rather than a direct

Definition of periodontal status	Hypertension/Blood pressure assessment	Strength of the association after adjustment	Main conclusions
Periodontitis as CPITN score of 3–4	Measurements of BP using a standard mercury sphygmomanometer. The definition for AH was as follows: SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg or taking antihypertensive drugs.	• OR: 1.34, (95% CI = 1.14–1.58) for periodontitis and AH (adjusted model). • OR: 1.23 (95% CI = 1.06–1.42) in the propensity score-adjusted analysis	Periodontal disease is significantly and positively correlated with increased risk of AH in the Chinese population

effect of the bacteria themselves. Peripheral neutrophilic polymorphonuclear leukocytes from patients with periodontitis produce higher levels of reactive oxygen species[96] than healthy controls. Intriguingly, periodontal treatment can reduce the hyper-reactivity of polymorphonuclear cells in response to inflammatory stimuli, but the unstimulated hyperactivity remains, suggesting that both constitutive and reactive mechanisms underlie neutrophil hyperresponsiveness in periodontitis.[97]

The mechanisms underlying the association between periodontitis and atherosclerotic disease have recently been described in an excellent review.[6] Briefly, they can either be attributed to the microbial presence per se or to the associated immune-inflammatory response or both, since periodontal pathogens can indeed reach atherosclerotic plaques transported by monocytes/macrophages and dendritic cells (the "Trojan Horse" approach). Within these cells, *Pg* can exert pro-atherosclerotic activities by inducing the oxidation of the engulfed lipoproteins and the production of pro-inflammatory cytokines.[98]

At the site of endovascular injury, the interaction of *Pg* with vascular endothelial cells through its adhesins, including FimA[99] and HagB,[100] drives its incorporation via the autophagosome.[101] By engaging the autophagy machinery, *Pg* preserves its virulence and can persist, alive, within the cell.[102] Once there, it drives the generation of oxidative stress through the activation of the TLR-NFkB signaling pathway and the NLRP3 inflammasome, and the generation of the nitrifying stress through its impact on the NO-producing enzymes (downregulation of eNOS and upregulation of iNOS). The proteolytic activity of the specific gingipains destroys the endothelial barrier by affecting the cell–cell junction molecules (VE-cadherin, N-cadherin, PECAM-1, and integrin β1) and leads to the death of endothelial cells via the activation of caspases 3, 8, and 9 and the cleavage PARP and TOPOI.[103] Furthermore, the lipopolysaccharide of *Pg* can promote the transition from the endothelial to the mesenchymal phenotype, through the regulation of p38, Erk1/2, and p65.[104]

Globally, the persistence of *Pg* can impact the biology of cardiovascular tissue as well as the immune response associated with ASCVD (as recently reviewed by Zhang et al[105]). Some specific serum antibodies elicited by periodontal pathogens may cross-react with autoantigens.[106] Interestingly, beyond the local effects at sites of cardiovascular injury, in vivo studies suggest a reciprocal effect between the function of the autonomic nervous system and periodontitis. Ligature-induced experimental periodontitis drives a sympathetic overactivity[107] eventually causing global cardiac dysfunction. In turn, stimulation of the carotid sinus nerve[108] appears to exert a beneficial effect on the extent of inflammation and alveolar bone loss in experimental periodontitis.

3.3 | Preclinical studies

Preclinical studies are crucial for establishing a direct causal link between periodontitis and ASCVD. Animal models can be used to explore the impact of periodontitis on the risk and prognosis of acute cardiovascular events. Several methods can induce periodontitis in mice, including using ligatures only, *Pg* bacteria only,[109] ligatures with *Pg*,[110] or a polymicrobial infection.[111] The induction of periodontitis by oral gavage of *Pg* for 2 weeks increased the severity of atherosclerosis in apolipoprotein E knockout mice, linked to a profound modification of the gut microbiota and the use of a high-fat diet.[112] A polymicrobial infection obtained by concomitant inoculation of four periodontal bacteria (*P. gingivalis*, *T. forsythia*, *T. denticola*, *and F. nucleatum*) in the gingival sulcus of the mice aggravates atherosclerosis by altering systemic immune and lipid pathways.[113] The polymicrobial oral infection model is more relevant to human disease than the model based on oral administration of *Pg* alone as it mimics the complex microbial community and dysbiosis seen in human periodontitis. The use of this method in humanized mouse models can reflect the human immune system and its interaction with oral bacteria,[114] however, they cannot fully capture the complexity and diversity of human periodontitis and CVD.[115] As a result, there is no definitive answer to which the periodontitis model is more relevant to human disease, but rather different models may have different advantages and limitations based on the research question and objective.[116]

3.4 | Clinical studies supporting the biological plausibility

Clinical studies remain useful to explore the biological mechanisms between periodontitis and cardiovascular diseases in humans, especially at the complications stage (stroke and MI). For example, in cerebrovascular diseases, the role of intraplaque hemorrhage in the

vulnerability of atheromatous plaques to rupture is well established, and periodontal pathogens (either themselves or their by-products) may be silent triggers. An ex vivo study in 157 patients undergoing carotid endarterectomy has shown that intraplaque hemorrhage and hemoglobin levels were associated with neutrophil activation, cell-free DNA, neutrophil extracellular traps, and *T. forsythia*, respectively, suggesting a potential role of periodontal microorganisms in neutrophil activation within hemorrhagic atherosclerotic carotid plaques.[117] In a retrospective study, the level of periodontal inflammation as assessed by 18F-FDG-PET/CT was found to be independently associated with the occurrence of subsequent major cardiovascular events.[33] In addition, a cross-sectional study in 45 periodontitis patients admitted for carotid endarterectomy, found that periodontitis, defined by attachment loss and anti-*Pg* antibody levels, was significantly associated with neutrophil activation markers and plaque vulnerability to rupture.[118]

A recent meta-analysis performed by the Cochrane Oral Health Information Specialists[119] concluded that the currently available data from interventional studies in patients are not adequate to support a role for periodontal therapy in the secondary prevention of ASCVD, while the evidence for an effect of primary prevention is lacking.

Holmlund et al. showed that periodontal disease and its response to treatment may have implications for cardiovascular health. They suggest that periodontal treatment may reduce systemic inflammation and improve endothelial function, which may lower the risk of CVD.[120] Furthermore, they also showed that a poor response to periodontal treatment is associated with a higher incidence of fatal/nonfatal cardiovascular events.[121] The authors suggest that the poor response to treatment may imply a systemic inflammatory burden that increases the risk of cardiovascular complications. However, they also acknowledge that more studies are needed to confirm the causal relationship between oral health and CVD.

This kind of study is important but unfortunately, it does not allow firm conclusions to be drawn because either there is no control (e.g., indirect assessment of the periodontal or the cardiovascular condition, or even self-reported parameters) or it is controlled but uses surrogate biomarker outcomes. Another potential source of bias is the ongoing medical treatments.[122]

It has, for instance, been reported that oral hygiene behavior (self-reported toothbrushing frequency and dental checkups) is associated with reduced overall risk of ASCVD-related death.[123] The effect of periodontal treatment on ASCVD risk factors, such as arterial blood pressure,[58] or surrogate markers, such as brachial artery flow-mediated vasodilation, has been reported in patients with stable coronary artery disease[124] or after a myocardial infarction.[125] Differences in surrogate biomarkers of ASCVD were observed in patients with diabetes[126] but not in patients with stable coronary artery disease.

The main issues concern the duration of follow-up and the size of the patient population that is required to observe ASCVD events in prospective studies. To circumvent these logistical barriers, a small randomized controlled study, currently ongoing in France (namely Parocard, ClinicalTrials.gov Identifier: NCT04046237), was designed to assess the effect of complete periodontal treatment on the inflammatory status of potential culprit atherosclerotic plaques, 1 year after an acute myocardial infarction. Of note, the extent of the atherosclerotic plaque inflammation is directly linked to the occurrence of ASCVD, as suggested by a recent clinical interventional trial (CANTOS).[127]

4 | CLINICAL EVIDENCE OF THE RELATIONSHIP BETWEEN PERIODONTITIS AND ASCVD

This section aims to describe the efficacy and effectiveness (cost/benefit) of periodontal treatment on cardiovascular events and/or cardiovascular risk factors both in otherwise healthy patients (primary prevention) and in patients with history of ASCVD (secondary prevention). As previously mentioned, the clinical evidence discussed in the following section comes from an update of the literature search (Table S3) performed in the latest narrative reviews published in 2020 in Periodontology 2000. Therefore, the results of interventional studies conducted in adults over 19 years of age, published and available since February 2019 (randomized and nonrandomized clinical studies), were selected and summarized in Table 4.

4.1 | Definition of periodontal interventions

First, interventional studies face the ethical issue of the type of control group, that is, not treating a patient with ongoing periodontitis is not acceptable. Common procedures for the control group are often called "delayed periodontal treatment" or "community-based periodontal treatment." In the delayed protocol, controls may receive oral hygiene instructions and supragingival mechanical plaque removal in one session or no treatment during the study protocol (so-called "no treatment" group in some studies). Generally, controls are offered conventional periodontal treatment after the completion of the study. In the community treatment protocol, controls are managed by their dentist (general dental practitioner) according to current clinical practice, thus in a clinical setting that can vary according to the local reimbursement policies for periodontal care and the specific professional organization (hygienists or not). Basically, the test group benefits from "intensive" periodontal treatment including all steps of periodontal therapy necessary to treat periodontitis stages I to II, as recently defined by the EFP S3 level clinical practice guideline.[128] These include oral hygiene instruction, professional mechanical plaque removal, subgingival instrumentation (in one session or per quadrant), sometimes adjunctive systemic or local antimicrobials, periodontal surgery with extraction of hopeless teeth (if needed), and regular periodontal follow-up along the duration of the study.

4.2 | Effects of periodontal therapy in preventing cardiovascular events

To address the question "Is there an effect of periodontal treatment in preventing or delaying ASCVD events?", the experts in cardiology and periodontology of the last joint workshop concluded that the progression of ASCVD may be influenced by successful periodontal treatment independently of traditional ASCVD risk factor management.[2] They based their conclusion on consistent evidence coming mainly from observational studies and highlighted the ethical and methodological complexity, let alone the high costs of running RCTs with sufficient power to test the efficacy of periodontal treatment at the general population level (primary prevention). Hence, none of the interventional studies published since 2019 investigated the efficacy of periodontal treatment on major adverse cardiac events, that is, myocardial infarction, stroke, or cardiovascular death as a primary outcome, either in the general population or in ASCVD patients (secondary prevention). However, an observational study was published in 2019 and provided new insights concerning secondary prevention. Santos-Paul et al. investigated whether periodontitis treatment improved the cardiovascular prognosis of patients with advanced kidney disease awaiting transplantation.[129] They compared the incidence of cardiovascular events and death among patients treated for periodontal disease when indicated to a historical cohort of patients who did not have this oral care protocol. In this population, at high cardiovascular risk, the association between periodontal treatment and cardiovascular events/death was statistically significant with an HR reduction of over 50% after controlling for several confounders.

Based on the present critical appraisal of the most recent literature, we can confirm the conclusion of the previous EFP and World Heart Federation consensus highlighting that there is only limited evidence for a beneficial effect of periodontal treatment for preventing cardiovascular events in patients with and without comorbidities. In the same vein, Ye et al. included only two RCTs in their last update of the Cochrane systematic review based on the following PICO question: "What are the effects of periodontal therapy for primary or secondary prevention of CVD in people with chronic periodontitis?".[130] The inclusion criteria were CVD-related death, all-causes death, or CVD events as primary outcomes, and RCTs with at least 12 months of follow-up. The two included studies were classified at high risk of bias according to the RoB-2 tool. The first RCT ($n = 165$) evaluated ASCVD events in patients with periodontitis and metabolic syndrome (primary prevention).[131] Since only one death was reported during the 1-year study duration, it was not possible to ascertain whether the periodontal treatment (i.e., scaling and root planing) plus the adjunctive administration of systemic amoxicillin and metronidazole increased or decreased the risk of cardiovascular events. The level of evidence for this RCT was rated as very low (GRADE assessment tool). The second included RCT ($n = 303$) is the well-known Periodontitis and Vascular Events (PAVE) pilot study exploring ASCVD events in patients with history of CVD defined as more than 50% blockage of one coronary artery or a history of a coronary event and periodontitis (secondary prevention).[115] Finally, these data were not included in the Cochrane Library meta-analysis because the length of follow-up was heterogeneous (6 to 25 months) with only 37 patients completing the 1-year follow-up. Also, this trial was judged to be of very low quality.

To date, it remains unknown whether periodontal treatment can be an efficient primary and secondary preventive strategy for ASCVD. Moreover, the mechanisms of action by which periodontal therapies would influence the course of CVD are still unclear; they are supposed to be linked with the reduction in the systemic inflammatory burden, the improvement in blood pressure, and the control of shared modifiable risk factors (e.g., tobacco and diabetes). This uncertainty may explain why cardiologists have not yet integrated a systematic periodontal evaluation and care into their routine practice. As expected, recent interventional studies selected different physical and/or biological surrogate markers for cardiovascular events to test the efficacy of periodontal therapy both in otherwise healthy patients and in patients with cardiovascular risk factors.

4.3 | Effects of periodontal therapy on cardiovascular parameters

In 2019, a single-center, parallel-group, randomized clinical trial was conducted to investigate whether an intensive periodontal therapy (i.e., full-mouth subgingival and supragingival scaling plus the application of a 0.2% chlorhexidine gel) compared to a control periodontal therapy would reduce blood pressure (BP) (primary outcome), vascular parameters, and inflammatory cytokines (secondary outcomes) at 2 months.[58] The difference in blood pressure changes from baseline between the controls and the intensive periodontal treatment group was 11.1 mmHg (95% CI 6.5–15.8) for the systolic component and 8.3 mmHg (95% CI 3.98–12.6) for diastolic one. Unsurprisingly, patients under 58 years old benefited the most from the treatment of their periodontitis in terms of BP reduction. Changes in the endothelium-dependent vasorelaxation (assessed by the brachial artery flow-mediated dilatation, FMD) between baseline and 2 months following treatment were + 2.4% (95% CI: 1.4–3.4) and + 0.7% (95% CI: 0.04–1.5) for the intensive periodontal therapy and control group, respectively. Interestingly, the greater the changes in the periodontal pocket depth greater the benefits in terms of blood pressure reduction. Moreover, after adjustment, INF-ɣ and IL-6 blood levels were significantly lower in the intensive periodontal treatment group than in the control group. In conclusion, this RCT provided a proof of concept supporting periodontal treatment as a nonpharmacological therapeutic strategy in hypertension. However, the results should be interpreted with caution due to the short duration of the study.

In 2020, a RCT aimed to evaluate the impact of periodontal treatment on the endothelial function of patients with a recent ST-segment elevation myocardial infarction (STEMI) at 6 months of follow-up.[125] Conducting such a RCT in post-infarction patients is a challenge. The

TABLE 4 Update on interventional studies conducted in adults investigating the association between periodontitis and ASCVD events (May 24, 2023).

Publication/country	Journal	Study design	Population	Intervention group
Czesnikiewicz-Guzik et al. 2019/ Europe (Poland)	European Heart Journal	Single-center, parallel-group, randomized clinical trial (NCT02131922)	Hypertensive patients with moderate/severe periodontitis; definition of hypertension: receiving stable treatment using at least one antihypertensive agent, for at least 6 months, and had an office BP of >140/90 mmHg at the time of visit; definition of periodontitis: Center for Disease Control–American Association of Periodontology case definitions	***n* = 50** (median age 53, men 52%, type 2 diabetes 8%), intensive nonsurgical periodontal treatment (IPT; whole-mouth subgingival and supragingival scaling of the teeth using also 0.2% chlorhexidine gel)
Santos-Paul et al. 2019/South America (Brazil)	Clinical Transplantation	Single-center, **retrospective cohort (Ki-Heart) study**	Population of **hemodialysis patients** included on the waiting list for renal transplantation; 60% with coronary artery disease; 74% with moderate/severe periodontitis defined by clinical attachment level 3–4 mm, and ≥5 mm, respectively	***n* = 206** (mean age 52.6, men 65%, diabetes 50%) thorough debridement of the affected root surfaces or tooth extraction, as indicated, and any other type of treatment considered suitable (plaque control, caries, endodontic intervention). Prophylactic antibiotics were not used. All patients were given instructions in basic oral hygiene. Patients were then referred to generalists for continuing dental health assessment
Lobo et al. 2020/ South America (Brazil)	European Journal of Internal Medicine	**Randomized controlled trial** (NCT02543502)	Patients with a **recent ST-segment elevation myocardial infarction** and **with severe periodontal disease**. Definition of STEMI: typical chest pain at rest associated with ST-segment elevation, or typical pain at rest in patients with a new, or presumably new, left bundle-branch block. Definition of severe periodontal disease: clinical attachment loss ≥4 mm and subgingival probing depth ≥6 mm in at least 5 teeth, associated with gingival bleeding in at least 8 teeth (according to Page and Eke 2007)	***n* = 24** (mean age 55.2, men 64%, diabetes 50%), periodontal treatment, including oral hygiene instructions, professional supragingival plaque, and calculus removal, remains roots extractions, treatment of carious teeth, 14 days after one to four sessions of subgingival instrumentation, then 3 month and 6 month (end of the study) follow-up periodontal visit with instrumentation if needed

Control group	Cardiovascular outcome(s)	Study duration and patients lost during follow-up	Result(s)	Authors' comments and conclusions
n **= 51** (median age 56, men 60%, type 2 diabetes 11%), control periodontal treatment (CPT; supragingival scaling)	**Primary outcome**: mean ambulatory 24-h SBP **secondary end points**: vascular function (FMD of the brachial artery and nitroglycerine-mediated dilatation); inflammatory soluble and cellular biomarkers	**2-month** follow-up; in both groups, 5 patients did not reach the 2-month time point and were lost to follow-up (intention-to-treat analysis)	Substantial **reduction in mean SBP** in IPT compared to the CPT with mean difference of −11.1 mmHg; 95% CI 6.5–15.8; $p < 0.001$; Reduction in mean level of IFN-gamma in IPT compared to the CPT with mean difference in change of 10.4 pg/mL Reduction in mean level of IL-6 in IPT compared to the CPT with mean difference in changes: 6.0 pg/mL, no differences were noted in the other circulating biomarkers No serious adverse events were reported	• IPT was associated with a 7.5 ± 10 mmHg reduction in BP. This could represent an important health change linked to prevention of hypertension complications. • A longer follow-up of 6 or 12 months would be needed to allow for therapeutic recommendations and conclusions.
n **= 203** (mean age 55.2, men 64%, diabetes 50%), included in the cohort during a 24-month period immediately preceding the initiation of routine oral examination in the study cohort. Controls underwent similar clinical evaluation, with the exception of the oral examination (treatment)	**End points**: composite incidence of ASCVD events (myocardial infarction, unstable angina, stroke, sudden death, heart failure, gangrene, or acute peripheral arterial syndrome), coronary events (myocardial infarction, unstable angina, and sudden death), CV death (myocardial infarction, sudden death, stroke, heart failure, death related to coronary intervention, gangrene/acute peripheral arterial syndrome), and death by any cause	**24 months** or until death or transplantation, no patient lost to follow-up	The incidence of adverse events was high, close to 10% per year; after adjustment on age, sex, smoking, dyslipidemia, diabetes, CVD, time on dialysis, and previous coronary intervention, oral evaluation followed by treatment was an independent predictor of **reduction in CV events** (HR 0.43, 95% CI: 0.22–0.87), **coronary events** (HR 0.31, 95% CI: 0.12–0.83), and **CV deaths** (HR 0.43; 95% CI: 0.19–0.98).	• In this high CVD-risk population (advanced renal disease), treatment was associated with a reduction in the incidence of ASCVD events.
n **= 24** (mean age 55.2, men 64%, diabetes 50%), no periodontal treatment but periodontal treatment was offered to the patients in the control group after the end of the study	**Primary end point**: 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**: cardiovascular events (death, myocardial infarction, stent thrombosis, and urgent revascularization), adverse effects (bacteriemia) of periodontal treatment and inflammatory markers including serum levels of IL-1β, IL-6, and IL-10.	**6-month** follow-up	Significant **FMD improvement in the intervention group** (3.05%; $p = 0.01$), but not in the control group (−0.29%; $p = 0.79$) ($p = 0.03$ for the intergroup comparison). Inflammatory profile and cardiovascular events were not significantly different between both groups	Treatment of periodontal disease improves the endothelial function of patients with a recent MI without adverse clinical events. Benefit of periodontal Larger sample size of trials is needed to assess the treatment on strong cardiovascular clinical outcomes.

(Continues)

TABLE 4 (Continued)

Publication/country	Journal	Study design	Population	Intervention group
Escobar Arregocés et al. 2021/ South America (Colombia)	Medicine	**Before-and-after (nonrandomized) study**	**Controlled hypertensive patients with periodontitis** stage II to IV, grade A and B	***n* = 19** (mean age 57.6, men 47%, no diabetes), all patients received oral hygiene instruction and nonsurgical periodontal treatment (scaling and root planing) with ultrasonic piezoelectric and Gracey curettes in 1 session.
Okada et al. 2021/ Asia (Japan)	PlosOne	**Parallel group, open-label randomized controlled trial** (IDUMIN000023395)	**Otherwise, healthy patient with early-stage periodontal disease**; definition of periodontitis: ≥2 sites with bleeding on probing (BOP) or a probing pocket depth (PPD) of ≥4 mm at ≥1 site	***n* = 56** (median age 38, men 67%, no diabetes), all periodontal patients received standard care for periodontal diseases under local anesthesia if required, including same-day full-mouth scaling and polishing with nutritional and exercise guidance in addition to basic oral hygiene instructions, the same toothpaste and toothbrush were given to each participant every month with counseling (2 brushing sessions per day); the test group had to use hypochlorous acid water, an electrolyzed disinfectant with a custom-made prescription tray after their standard self-care

estimated sample size was 88 patients based on previous literature. However, the recruitment rate was lower than initially expected due to a high percent of patients not meeting the inclusion criteria. Limiting operational aspects was also important and probably underestimated, in particular the need for a systematic evaluation of periodontal disease in patients hospitalized for an acute MI with several other medical and personal constraints to deal with other than the oral health examination. For these reasons, the authors had to stop their clinical trial prematurely after including only 48 patients, lowering the statistical power of the RCT to 67%. At 6 months, endothelial function evaluated by the FMD of the brachial artery improved significantly only in patients receiving periodontal treatment (from 9.0 ± 4.4% at baseline to 12.1 ± 5.6% at follow-up; $p = 0.01$) (no statistically significant change in the control group). Concerning the secondary end points, no significant variation in serum IL-1β, IL-6, and IL-10 levels between baseline and 6-month follow-up was observed.

Finally, in 2021, two studies with different designs and quality (one small observational before-and-after study,[132] and one RCT[133]) were published, all aiming to answer the question of whether periodontal therapy influences surrogate cardiovascular markers in patients with and without a history of ASCVD (primary and secondary prevention). IL-1β and blood levels of vascular endothelial growth factor were significantly reduced at 4 to 5 weeks after nonsurgical periodontal treatment in 19 controlled hypertensive patients studied without randomization or a comparator group.[132] In this study, no significant blood pressure variation was observed at 1 month after one session of full-mouth periodontal debridement. These results should be carefully interpreted because of the low-quality study design, the small sample size, and the short follow-up. Okada et al. performed an RCT to evaluate at 3 months the effects of advanced self-care on atherosclerotic cardiovascular disease-related vascular function markers, brachial

Control group	Cardiovascular outcome(s)	Study duration and patients lost during follow-up	Result(s)	Authors' comments and conclusions
	Primary outcome: serum levels of inflammation biomarkers including interleukin 1-b, interleukin-4, interleukin-6, interleukin-8, interleukin-10, interleukin-12 P70, interleukin-17A, vascular endothelial, growth factor and tumor necrosis factor-alpha; **secondary outcome**: blood pressure	**4 to 5 weeks** after the periodontal treatment, 3 patients were excluded from the study because of incomplete follow-up	Mean level of **IL-1β and VEGF decreased significantly after treatment** from 0.53 ± 0.14 to 0.30 ± 0.07 in pg/mL with *p* value = 0.04 and 152.10 ± 28.7 to 101.55 ± 18.36 in pg/mL with *p* value = 0.004, respectively; • **No statistically significant difference in mean blood pressure** before and after periodontal treatment, 135.15/86.1 mmHg and 133.26/83.15 mmHg, respectively	Nonsurgical periodontal treatment decreases the levels of systemic proinflammatory cytokines in hypertensive patients.
***n* = 54** (median age 37, men 54%, no diabetes), all periodontal patients received standard care for periodontal diseases under local anesthesia if required, including same-day full-mouth scaling and polishing with nutritional and exercise guidance in addition to basic oral hygiene instructions, the same toothpaste and toothbrush were given to each participant every month with counseling (2 brushing sessions per day); the control group received no extra intervention than the standard self-care	**Primary outcome**: changes in FMD between baseline and 3 months; **Secondary outcomes**: change in serum asymmetric dimethylarginine (ADMA; an endogenous nitric oxide synthase inhibitor)	**3-month** follow up	**In intention-to-treat analysis, no significant improvements in FMD** were observed in the control or test groups. No significant between-group difference was detected (mean difference, −0.2%; 95% CI: −1.4–0.9; *p* = 0.708); **No significant improvements in serum ADMA** levels were observed in either control group or test group, with no significant between-group difference observed (mean difference, 0.01 nmol/L; 95% CI, −0.00–0.03; *p* = 0.122); **no severe adverse events** were observed during the trial.	Advanced periodontal self-care for 3 months did not significantly improve FMD as compared to standard care in patients with early-stage periodontal diseases.

artery FMD, and serum asymmetric dimethylarginine (ADMA) level in patients with early-stage periodontal disease compared to otherwise healthy patients.[133] In this study, the periodontitis case definition was at least two sites with bleeding on probing or one site with a probing pocket depth of ≥4 mm. These cut-off values cannot be specific to even early stage periodontitis, and it is likely that gingivitis cases were also potentially included and treated in this study. All the participants received the standard of care for periodontal diseases including a same-day full-mouth scaling and prophylaxis with nutritional and basic oral hygiene instructions. The test group ($n = 56$) used a custom tray with antiseptic for the 3-month duration of the study, whereas the control group ($n = 54$) received no extra intervention. This periodontal treatment had no effect on FMD and ADMA, which are endogenous nitric oxide synthase inhibitors thought to be linked with hypertension progression.

To summarize, the quantity and the quality of evidence supporting the contention that periodontitis treatment positively impacts cardiovascular risk markers measured clinically, or laboratory tested, remains limited and it has only increased slightly since the last consensus report[2] or the last narrative reviews[4,5] (Table 5). Only one study investigated the cost-effectiveness of periodontal treatment in the prevention of stroke-associated pneumonia during the patient's rehabilitation using a health economic evaluation.[134] In stroke survivors, pneumonia is a frequent and severe complication with high healthcare costs and clinical consequences. These patients exhibit high oral microbiota loads due to swallowing difficulties and poor oral hygiene. The implementation of a high level of oral health care provided by nurses versus a standard oral health care protocol was hypothesized to reduce the incidence of stroke-associated respiratory complications. The cost in pounds of the enhanced oral healthcare protocol

TABLE 5 Additional evidence from studies on the efficacy of periodontal therapy on the reduction in cardiovascular risk markers (May 24, 2023).

Vascular MARKERS	Blood pressure	Endothelial function by flow-mediated dilatation	Arterial stiffness by pulse wave velocity	Intima-media thickness	Lipids	C-reactive protein	Inflammatory cytokines and biomarkers
State of the evidence in 2019[a]	Limited evidence of EFFECT	Moderate evidence of EFFECT	Limited evidence of NO EFFECT	Limited evidence of EFFECT	Moderate evidence of NO EFFECT	Moderate evidence of EFFECT	Moderate evidence of EFFECT
Studies reporting the end point	{Czesnikiewicz-Guzik, 2019 #16}{Escobar Arregocés, 2021 #13}	{Czesnikiewicz-Guzik, 2019 #16}{Lobo, 2020 #15} {Okada, 2021 #17}					{Czesnikiewicz-Guzik, 2019 #16}{Escobar Arregocés, 2021 #13}
Number of studies reporting an improvement in the end point/number of additional intervention studies from 2019	1/5	2/5	0/5	0/5	0/5	0/5	2/5
Change in state of the evidence in 2022	↑	↑↑	↔	↔	↔	↔	↑↑

[a]Reference: EFP and WHF workshop.

(including the salary of the trained nurses, the dental products, and resources) was calculated in comparison with the costs of the standard protocol for the cost-effectiveness analysis. However, in this feasibility study, the rate of pneumonia was lower than anticipated and prevented any conclusion on both the clinical and health economic levels. Finally, despite the increasing number of observational studies focusing on the atherosclerotic plaque microbiome[118] or gut microbiome analysis,[80] no interventional study has yet explored whether periodontal treatments modify the load and composition of the microbiome in patients with ASCVD.

5 | THE RELATIONSHIP BETWEEN PERIODONTITIS AND ASCVD: AN UNDERLYING CAUSAL LINK?

As reviewed above, the literature supports an independent association between periodontitis and ASCVD. However, there is still a debate as to whether periodontitis should be considered as a marker or an indicator of risk (i.e., associated but not causally linked) or as a risk factor (i.e., a causal factor for ASCVD).

Prospective cohort studies could bring some insights into causality, although RCTs are the cornerstone design to assess a causal relationship (Table 6). To date, there are no RCTs supporting a causal relationship between periodontitis and ASCVD events, although many RCTs show that the treatment of periodontitis improves surrogate markers of ASCVD.

Causal inference has been clearly defined through the classical nine Bradford Hill's criteria, where all must be satisfied.[136] As shown in Box 4, not all the criteria that define causality are met when dealing with the relationship between periodontitis and ASCVD. An interesting causal approach based on the Rothmans "sufficient cause" model has been recently proposed in commentary.[140] The root of causal inference lies in Koch's postulates, and it is based on the paradigm that one exposure produces one outcome, that is, one cause produces one effect. Bradford Hill's criteria are consistent with the cause–effect pattern. However, when dealing with multifactorial diseases, a single cause may not be sufficient to trigger the disease. Furthermore, a single causal mechanism is unlikely. Rothmans identified two types of causes: (1) the necessary cause, a prerequisite for the outcome to occur; and (2) the sufficient cause, a set of exposures that inevitably produce the outcome.[141] Each exposure of the sufficient cause model may be involved in several causal mechanisms but not all the potential causal mechanisms. It can be hypothesized that periodontitis is one of the exposures that belongs to the sufficient cause of ASCVD, that is, periodontitis could be a component cause of ASCVD. This approach would also explain the fact that there is little chance of identifying the effect of periodontal treatment in reducing the incidence of ASCVD events.

Finally, Mendelian randomization[§] may provide evidence supporting a causal relationship between periodontitis and ASCVD. If genetic

[§]Mendelian randomization (MR) is an analytical approach that uses genetic variants as instrumental variables to assess causal relationships between an exposure (such as a risk factor or trait) and an outcome (such as a disease).

TABLE 6 Level of evidence according to the typology of the risk factor (adapted from Bouchard et al. 2017).[135]

CAUSALITY		Evidence of Biological link	Study design				
			Case Report / Case Series	Case-Control Study	Cross-sectional Study	Longitudinal Cohort Study	Randomized Clinical Trial (when applicable)
	True Risk Factor*	Established	✓	✓	✓	✓	✓
	Risk Indicators **	Putative	✓	✓	✓		
	Predisposing Factors	Not Established	✓	✓	✓		

Note: Synonyms: *classical risk factor, traditional risk factor, or established risk factor; **risk marker and putative risk factor.

BOX 4 Causality assessment between periodontitis and ASCVD according the Bradford Hill criteria.

1. *Strength of the association*: **YES/NO**
   - Weak to modest
2. *Consistency*: **YES**
   - A relationship is repeatedly observed in almost all available studies.[4]
3. *Specificity*: NO
   - The studies failed to demonstrate the same outcome in every instance.[123]
4. *Temporality*: NO
   - Lack of demonstration that periodontitis always precedes the ASCVD event.
5. *Biological gradient*: **YES**
   - The more severe the periodontitis, the higher incidence of ASCVD events.[137]
6. *Plausibility*: **YES**
   - Several plausible biological mechanisms have been suggested.[6]
7. *Coherence*: **YES**
   - Inflammation has a central role in ASCVD.[138]
8. *Experiment*: NO
   - Lack of RCTs supporting the causal role of periodontitis in the occurrence of ASCVD events.
9. *Analogy*: **YES**
   - For instance, periodontal treatment reduce the HbA1c levels, which is associated with an increased risk of cardiovascular disease.[139]

variants associated with periodontitis are also associated with ASCVD, this supports evidence of a causal relationship. Moreover, Mendelian randomization can estimate the magnitude of the causal effect. Nevertheless, causal inference today cannot be supported by Mendelian randomization alone, but also by observational studies, randomized controlled trials, and mechanistic research.[58]

Perhaps the most important question related to this association is not causality. The question of whether the relationship between periodontitis and ASCVD is causal must, of course, be asked, but its relevance is challenged by the "common ground" hypothesis that will help to better identify the future the common genes to the two diseases. The concept of the "common soil" hypothesis postulates that common risk factors may lead to both periodontitis and ASCVD. In this perspective, periodontitis would not be a contributing cause of ASCVD but one of the multiple clinical manifestations of the shared risk factors. This could inaugurate a bidirectional prevention approach, with not only the periodontal patient being at risk of ASCVD but also the patient at risk of ASCVD being at risk of periodontitis. The "big bang data", that is, the explosion of causal analysis of genomic, transcriptomic, proteomic, and metabolomic data, that is, omics techniques, combined with advanced analytical techniques, such as machine learning and predictive data modeling, should help in the near future to understand the common risk factors between the two conditions.

To summarize, based on Bradford Hill's criteria, no conclusion can be drawn on the causal relationship between periodontitis and ASCVD. The "common soil" hypothesis, as well as the "sufficient cause" model, can be advocated to explain the concomitance of disease-specific risk factors. However, both models rely on a key issue: the temporal relationship between the exposures and the outcome, and, to date, there is no evidence that periodontitis precedes ASCVD.

6 | THE IMPACT OF PERIODONTAL HEALTH IN THE PREVENTION OF ASCVD

Risk prediction is a cornerstone of prevention strategies. Today, the ASCVD risk associated with periodontal status is not quantified. However, at each level of prevention, there is some evidence to suggest that this risk exists. In addition, although no conclusion can be made regarding the direct impact of periodontal therapy on the prevention of the onset or recurrence of ASCVD, there is some evidence that improved oral hygiene may reduce the risk of ASCVD.

Primordial prevention aims at preventing the development of risk factors in individuals who do not have the disease. It has been emphasized as a complementary prevention strategy for CVD. In other words, if periodontitis is a risk factor for ASCVD as suggested above, prevention of periodontitis, which is based on good oral health maintained by adequate oral hygiene, can contribute to preventing the risk of ASCVD in the general population. Observational studies indicate that oral hygiene and/or dental prophylaxis reduce the risk of ASCVD.[123,142,143] Recently, a cross-sectional analysis of 5430 individuals without a history of ASCVD suggests that adults with a preserved chewing capacity have an increased likelihood of being in an ideal behavioral state for cardiovascular health.[26]

Primary prevention aims at preventing the occurrence of the disease in individuals who do not have the disease but already have known risk factors. Again, if periodontitis is a known risk factor for ASCVD, treatment of periodontitis should decrease the risk of first MACEs. This is suggested, as described above, by both observational and interventional studies. Nevertheless, these studies only "suggest" an effect due to the lack of solid, long-term RCTs to prove the effectiveness of periodontal interventions on ASCVD. The feasibility of such a study demonstrating that the treatment of periodontitis results in a reduction in ASCVD is questionable. For instance, diabetic patients without history of CVD are already at risk for CVD because of their diabetes. If we hypothesize a study on this population, diabetic patients with periodontitis and without CVD should be divided into two groups, one receiving a periodontal treatment (test group), and one receiving at best a standard of care (control group). As a study end point, the between-group difference in the occurrence (incidence) of CV events (MI, Stroke, and PAD for instance) should be recorded. It is perfectly understandable that this type of study is prone to serious problems. First, an ethical one. The lag between baseline and the moment of the CV event is counted in years, and it is unethical not to treat periodontitis once diagnosed, particularly in populations at risk of adverse systemic health outcomes to be robust, this type of study should include an extremely large sample of patients followed-up for a long period. Finally, taking into account the above considerations, this type of study is prohibitively expensive. Consequently, it is not surprising that there is no RCT on primary prevention evaluating the effect of periodontal treatment in non-CV patients.

Secondary prevention aims at preventing the recurrence of the disease in individuals who have already experienced an event. For instance, an RCT should evaluate the efficacy of periodontal treatments in patients with a history of MACE. One pilot study in the USA failed to draw any conclusions about the effect of periodontal therapy on the secondary prevention of CVD.[144] A systematic review of the Cochrane database concluded there was insufficient evidence to support or refute the benefits of the treatment of periodontitis in preventing ASCVD events.[130]

Tertiary prevention aims at preventing the complications of an established disease in patients who have a chronic disease. No data are available on periodontal tertiary prevention of ASCVD.

Finally, a recent Japanese prospective observational study (median follow-up 28 months) conducted on a sample derived from the general population ($n = 692$) and including CVD patients showed that the combination of decreased frequency and duration of toothbrushing was associated with a significantly higher risk of MACEs and hospitalization for heart failure (HF).[145] Subjects who brushed their teeth less than twice/day and less than 2 min/procedure had a threefold higher rate of CV events during the study follow-up compared to subjects who brushed their teeth ≥ twice/day and ≥2 min/procedure. It is noteworthy that a 1-min increase in daily toothbrushing duration reduces the RR of CV events by 8% during follow-up. However, a limitation is that toothbrushing behaviors were self-reported.

Taken together, the above data suggest that periodontitis is a "residual" risk factor for ASCVD. Therefore, periodontitis has been included as a specific clinical condition that can influence CVD risk in the new sections of the ESC guidelines on CVD prevention.[146] However, the ESC guidelines also indicate that there is a gap in the evidence base to assess the efficacy of periodontitis treatment in preventing CVD, suggesting further large-scale trials.

7 | CLINICAL CONSEQUENCES (PREVENTION, ORAL HYGIENE AND PUBLIC HEALTH)

Hereafter, we discuss the risks linked to periodontal treatment and the implications for clinical practice and public health policies.

7.1 | Risks and complications of periodontal therapy

7.1.1 | Ischemia

There is evidence for a transient (1 week) increase in the inflammatory response and endothelial dysfunction after full-mouth nonsurgical periodontal therapy performed within 24 h,[5,147] and thus a pertinent question can be asked: "Is periodontal treatment safe for the cardiovascular health (ischemic risk) of patients with and without ASCVD history?". The latest joint EFP/WHF consensus concluded, based on limited evidence (two observational studies[148,149] and one self-controlled case series[150]) and expert opinions, that delivering periodontal treatment is safe with regard to cardiovascular risk at population level.[2,5] In patients with history of ASCVD, the expert consensus led to the same assumption: no evidence for ischemic effects of periodontal treatment. The experts essentially based their opinion on the PAVE pilot study[115] and one RCT,[151] both reporting no adverse events, or cardiovascular events over 3 months after periodontal therapy. The periodontal treatment consisted of (1) one session including oral hygiene instructions, supragingival plaque, and calculus removal; (2) four sessions of subgingival scaling and root planing

within maximum 2 weeks; and (3) a periodontal follow-up once a month. Since then, additional data have been published. Lobo et al. conducted an RCT on 48 patients with ST-segment elevation myocardial infarction and severe periodontitis. The periodontal treatment was not associated with acute adverse clinical outcomes, neither was bacteremia defined as the occurrence of fever >37.8°C in the first 24 h following the treatment, nor cardiovascular events such as death, myocardial infarction, stent thrombosis, or urgent revascularization.[125] Recently, a systematic review and meta-analysis was conducted to critically assess the available evidence on the link between invasive dental and periodontal treatments (nonsurgical periodontal therapy, surgical periodontal therapy, single, multiple, or wisdom tooth extractions, endodontic surgery, and dental implant placement) and cardiovascular events (defined as myocardial infarction, ischemic stroke, or both combined).[152] The authors concluded that invasive dental therapies do not increase the incidence of acute vascular events, at 1 month (1.02, 95% CI: 0.92–1.13) or 2 months (1.04, 95% CI: 0.97–1.10) post-therapy.[152]

7.1.2 | Hemorrhage

Regarding the bleeding risk of patients with ASCVD undergoing periodontal therapy, the joint EFP/WHF committee concluded overall a low level of risk.[2] Nevertheless, different categories of patients and periodontal procedures, as well as different levels of experience of dentists, may lead to variations in the bleeding risk of the patient. Periodontal interventions, including supragingival scaling, prophylaxis, subgingival debridement, periodontal surgery (conservative, resective, and regenerative), single tooth extraction, and dental implant placement, are considered at low risk of bleeding because they are associated with an occurrence of bleeding events of less than 1%. Conversely, bone grafting, multiple tooth extractions, and free gingival grafts are considered at high risk of bleeding with an occurrence of bleeding events between 2 and 5%. Neither antiplatelet medications (single or dual therapy) nor anticoagulant drugs have to be discontinued for periodontal therapy. The most common antiplatelet molecules, namely acetylsalicylic acid, clopidogrel, ticagrelor, and prasugrel, are prescribed in ASCVD (mainly in MI, stroke, or PAD) when the local thrombosis is the biological phenomenon to prevent. Vitamin K antagonists and direct oral anticoagulants are indicated when it is clot formation that leads to the risk, such as in AF (risk of sudden death), deep vein thrombosis, or heart valve diseases (valve prosthesis). Interestingly, in patients with old prosthetic models of mechanical valves only, the required level of anticoagulation is high with an international normalized ratio of up to 4, contra-indicating any periodontal surgery other than in a hospital setting. Direct oral anticoagulants are challenging for dentists planning periodontal surgery since no blood test is informative for the level of anticoagulation and they are associated with a higher incidence of delayed bleeding compared to patients without the drug. The decision to perform periodontal therapy in primary or secondary care settings should be based on a risk assessment as proposed by Leira et al. to prevent and manage complications and periodontal treatment errors.[153] The framework of the bleeding risk assessment is based on six domains addressing the different aspects of care such as access, communication, consent, education, surgery, and spread of infection, that is, the ACCESS tool. Briefly, the prevention and management of perioperative and post-operative prolonged bleeding rely on the following: (1) the proper use of local anesthesia (articaïne with vasoconstrictors), (2) minimization of the surgical trauma, (3) compression of the operative site with gauze dressing, (4) the use of hemostatic and antifibrinolytic agents (e.g., oxidized cellulose, gelatin foam, and tranexamic acid), (5) sutures, (6) post-operative prescriptions (e.g., avoid nonsteroidal anti-inflammatory drugs) and counseling (e.g., do not spit out), and (7) ease of access to a dental emergency unit (if needed). To summarize, the bleeding risk associated with periodontal treatments should not be neglected by the dental and medical team, however, the thrombotic risk is the main one to consider in ASCVD patients.

In most interventional studies, no adverse event including prolonged bleeding was reported, so the expected systemic benefits (on inflammatory burden and endothelial dysfunction) of periodontal therapy in ASCVD patients overcome the potential risks in terms of acute ischemic adverse events and bleeding.

7.2 | Recommendations for patients, oral care practitioners and medical care providers

An opportunistic preventive screening should be advocated in the dental setting. The dentist may use his/her contacts with the patients for exercising not only oral disease prevention but also the prevention of other prevalent diseases such as CVD. The expert group of the last joint EFP/WHF workshop made several recommendations for oral health professionals in three categories of patients: with periodontitis only, with ASCVD only, and with both diseases. A schematic summary is proposed in Figure 6. For physicians and other medical professionals, the recommendations are as follows: (1) to raise patient's awareness of the relationship between ASCVD and periodontitis; (2) to question the patient about a previous periodontitis diagnosis and check that appropriate management is undergone; (3) to look for key signs of periodontitis and symptoms (bleeding gums, loose teeth, tooth drifting, halitosis, and dental abscess) and to refer the patient to the dental surgery for evaluation and treatment; (4) to share any relevant medical information with the patient's dental surgeon to build a personalized treatment plan and prevent the bleeding risk associated with the pharmacological therapy prescribed.

Finally, thanks to the additional quantitative and qualitative evidence published since 2019, some practical recommendations

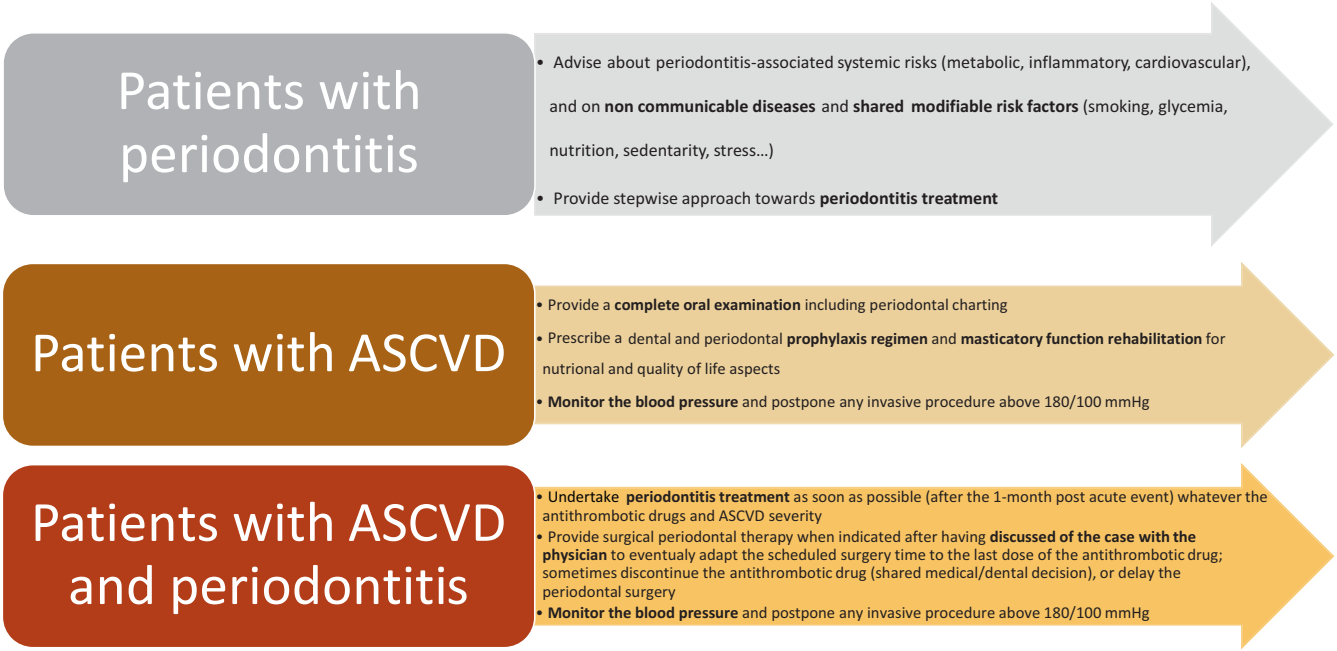

FIGURE 6 Proposal for a standard care pathway to improve prevention of ASCVD in dental settings based on the recommendations of the EFP/WHF consensus of 2019 (Sanz, Marco Del Castillo et al. 2020).

targeting specific categories of patients can be made. For instance, periodontal treatment should not be delayed in young and middle-aged patients who will benefit the most from it in terms of cardiovascular risk reduction.[58]

8 | PERSPECTIVES (FURTHER RESEARCH)

- There is a need for long-term interventional studies systematically reporting robust CVD outcomes (e.g., death and major adverse cardiovascular events), and surrogate and patient-centered outcomes (e.g., quality of life, satisfaction, and acceptability of the periodontal treatment).
- There is also a need to investigate the effect of treating periodontitis on inflammation within atheromatous plaques. The PAROCARD study, a clinical trial that aims to evaluate the impact of periodontal therapy on the inflammatory activity of atheromatous plaques in patients with severe periodontitis who survived an acute myocardial infarction,[¶] should be completed by the end of December 2024.
- The increasing popularity of connected tools applied to oral health, such as toothbrushes, is expected to enable the collection of big data, that is, real-world data (RWD).[**] The real-world evidence (RWE) from these data will better support public health decision-making as well as a personalized approach to preventive measures.
- Studies should be undertaken to better explore the relationship between periodontal disease and PAD. Similarly, the association between periodontitis and sudden death related to atrial fibrillation and hypertension is unknown.
- Authors should also investigate the cost-effectiveness of periodontal treatment in the management of ASCVD and its complications.

To conclude, poor oral health and periodontitis are independent factors associated with ASCVD. Still, there is no evidence of a causal link between periodontitis and ASCVD. However, a common risk hypothesis is relevant considering the current evidence. Consequently, dental professionals should be involved in the opportunistic preventive screening of ASCVD, and the reduction of oral inflammation.

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DATA AVAILABILITY STATEMENT

I confirm the absence of shared data

[¶] Impact of Treating Severe Periodontitis on Inflammatory Activity of Atheromatous Plaques in Patients With Acute Myocardial Infarction (AMI) – Full Text View – ClinicalTrials.gov

[**] https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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