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Periodontitis and cardiovascular diseases

Consensus report

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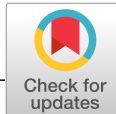
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Periodontitis and cardiovascular diseases: Consensus report

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Abstract

Background: In Europe cardiovascular disease (CVD) is responsible for 3.9 million deaths (45% of deaths), being ischaemic heart disease, stroke, hypertension (leading to heart failure) the major cause of these CVD related deaths. Periodontitis is also a chronic non-communicable disease (NCD) with a high prevalence, being severe periodontitis, affecting 11.2% of the world's population, the sixth most common human disease.

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Material and Methods: There is now a significant body of evidence to support independent associations between severe periodontitis and several NCDs, in particular CVD. In 2012 a joint workshop was held between the European Federation of Periodontology (EFP) and the American Academy of Periodontology to review the literature relating periodontitis and systemic diseases, including CVD. In the last five years important new scientific information has emerged providing important emerging evidence to support these associations

Results and Conclusions: The present review reports the proceedings of the workshop jointly organised by the EFP and the World Heart Federation (WHF), which has updated the existing epidemiological evidence for significant associations between periodontitis and CVD, the mechanistic links and the impact of periodontal therapy on cardiovascular and surrogate outcomes. This review has also focused on the potential risk and complications of periodontal therapy in patients on anti thrombotic therapy and has made recommendations for dentists, physicians and for patients visiting both the dental and medical practices.

KEYWORDS

anti thrombotic therapy, atherosclerosis, bacteremia, cardiovascular disease, chronic inflammation, periodontal therapy, periodontitis

1 | INTRODUCTION

Non-communicable diseases (NCDs) are rising in prevalence globally in line with an increasingly ageing population, refined diets and sedentary lifestyles and account for 41 million deaths each year, or 71% of all global deaths (G. B. D. Risk Factors Collaborators, 2016). Approximately 80% of people over 65-years of age in the United States are affected by one or more NCDs and 77% exhibit at least two NCDs, creating a significant burden of disease to individuals and to the healthcare economy (Centres for Disease Control & Prevention, 2011). The comorbid presence of two or more NCDs presents a major challenge to the economy, equating to two-thirds of all health costs in the United States (Centres for Disease Control & Prevention, 2013); however, <1% USA health expenditure is focussed on prevention to improve overall health (U.S. Senate Committee on Health, 2011).

The greatest global NCD burden arises due to cardiovascular disease (CVD), responsible for 17.9 million deaths (a third of total mortality), and 45% of NCD-induced mortality (Roth et al., 2017). In Europe, CVD is responsible for 3.9 million deaths (45% of deaths), and whilst CVD mortality rates are reducing, the absolute numbers have increased in the last 25 years, due to an increasingly ageing population (Wilkins et al., 2017). Ischaemic heart disease, stroke, hypertension (leading to heart failure), rheumatic heart disease, cardiomyopathy and atrial fibrillation cause over 95% of CVD-related deaths (Roth et al., 2015).

In this consensus report, the term CVD is used as a general term for atherosclerotic diseases, principally coronary heart disease, cerebrovascular disease and peripheral vascular disease. A number of chronic infectious, inflammatory and immune diseases are associated with significantly higher risks of adverse cardiovascular events,

including rheumatoid arthritis, psoriasis, systemic lupus erythematosus and periodontitis (Roth et al., 2015), consistent with the thesis that chronic elevations in the systemic inflammatory burden are causally related to CVD development and its sequelae. Whilst there is evidence for over 50 gene polymorphisms playing a role in the modulation of atherogenesis (Holdt & Teupser, 2015), effect sizes are small and the major traditional risk factors for CVD remain the lifestyle factors, principally tobacco smoking, dyslipidaemia, hypertension and altered glucose metabolism. The latter correlate strongly with diets high in saturated fats, salt and refined sugars and contribute to obesity and type 2 diabetes mellitus, major attributable risk factors for myocardial infarction (Joseph et al., 2017). The same risk factors account for over 90% of the stroke burden (O'Donnell et al., 2016), yet all are modifiable through improved lifestyles including reducing salt, saturated fat and refined carbohydrate intake, exercising, increasing intake of antioxidant micronutrients and regular moderate alcohol consumption (Joseph et al., 2017).

Periodontitis is also a NCD with a high prevalence of 45–50% overall, with the most severe form affecting 11.2% of the world's population, being the sixth most common human disease (Kassebaum et al., 2014). The Global Burden of Diseases, Injuries, and Risk Factors Study (2017) of years lost to disability (YLD) reported that from 1990 to 2017 oral diseases (mainly periodontitis and caries) contributed the most YLD in age-standardized prevalence rates from 354 diseases and injuries across 195 countries (G. B. D. Disease Injury & Incidence & Prevalence Collaborators, 2018). There is now a significant body of evidence to support independent associations between severe periodontitis and several NCDs including diabetes (Chapple, Genco, & Working group 2013 of the joint EFP/AAP Workshop, 2013), cardiovascular disease (Tonetti et

al., 2013), chronic obstructive pulmonary disease (Linden, Lyons, & Scannapieco, 2013) and chronic kidney disease (CKD) (Sharma, Dietrich, Ferro, Cockwell, & Chapple, 2016). Indeed, severe periodontitis is independently and significantly associated with all-cause and cardiovascular mortality in several different populations (Linden et al., 2012; Sharma et al., 2016). Proposed mechanisms include bacteraemia and the associated systemic inflammatory sequelae, including elevations in C-reactive protein and oxidative stress (Schenkein & Loos, 2013). In populations with multimorbidity, for example chronic kidney disease with comorbid diabetes and periodontitis, periodontitis is associated with significantly reduced survival from all-cause and cardiovascular mortality (Sharma et al., 2016). It appears therefore that periodontitis may be a modifiable non-traditional risk factor for CVD.

In 2012, a joint workshop was held between the European Federation of Periodontology (EFP) and the American Academy of Periodontology to review the literature relating periodontitis and systemic diseases, including CVD. The consensus report was based upon four technical papers that systematically reviewed the evidence for epidemiological associations between periodontitis and incident CVD (Dietrich, Sharma, Walter, Weston, & Beck, 2013), mechanisms of biological plausibility relating to periodontal bacteria and systemic inflammation (Reyes, Herrera, Kozarov, Roldan, & Progulsk-Fox, 2013; Schenkein & Loos, 2013) and periodontal intervention studies (D'Aiuto, Orlandi, & Gunsolley, 2013). The workshop concluded that there was consistent and strong epidemiological evidence that periodontitis imparts increased risk for future atherosclerotic cardiovascular disease. It also concluded that the impact of periodontitis on CVD was biologically plausible, via translocated circulating oral microbiota, which may directly or indirectly induce systemic inflammation that impacts upon the development of atherothrombogenesis, and whilst *in vitro*, pre-clinical and clinical studies supported the interaction and associated biological mechanisms, intervention trials were not sufficiently adequate to draw further conclusions at that time.

The present workshop was jointly organized by the EFP and the World Heart Federation (WHF) to include global experts in both periodontal and cardiovascular disciplines and was held in Madrid on 18th and 19th February 2019. Four technical reviews updating the evidence base from the 2012 workshop were prepared and supplemented by additional studies discussed at the workshop. The reviews focussed on epidemiological associations (Herrera, Molina, Buhlin, & Klinge, 2019), mechanistic links (Schenkein, Papananou, Genco, & Sanz, 2019), results from intervention studies (Orlandi, Graziani, & D'Aiuto, 2019) and the potential risk and complications of periodontal therapy in patients undertaking antithrombotic (antiplatelet and anticoagulant) therapy.

Whilst this consensus report focuses predominantly on relevant evidence published since the 2012 workshop, there are biological areas that have subsequently come to prominence, where the underpinning body of evidence was not covered in the 2013 consensus report, and hence, certain pre-2012 manuscripts are referenced to ensure the context of these recent studies is clear.

Furthermore, section 4.3 "What is the effect of statin intake on clinical periodontal outcomes?" and section 5 "Cardiovascular risks and complications of periodontal therapeutic interventions" were not dealt in the previous workshop, and hence, a full appraisal of the scientific evidence was carried out in this consensus meeting.

Finally, following the review of the presented evidence, recommendations for both medical and dental teams, as well as patients and the public, were elaborated.

2 | EPIDEMIOLOGIC EVIDENCE ON THE ASSOCIATION BETWEEN PERIODONTITIS AND CVD

2.1 | Do people with periodontitis have a higher prevalence of subclinical cardiovascular disease?

There is evidence from epidemiological studies that periodontitis patients exhibit significant endothelial dysfunction, measured by flow-mediated dilation (FMD), arterial stiffness (e.g. pulse wave velocity—PWV) and a significantly greater thickness of the carotid intima-media (cIMT) and elevated arterial calcification scores. There is one imaging study (ATHEROREMO-IVUS study) associating high levels of antibodies against periodontal pathogens and a lower extent of positive atheromatous plaque remodelling (de Boer et al., 2014).

2.2 | Do people with periodontitis have a higher prevalence of coronary artery disease and risk of myocardial infarction and other coronary events?

There is robust evidence from epidemiological studies for a positive association between periodontitis and coronary heart disease. A systematic review (Dietrich et al., 2013), which was updated in preparation for this workshop, identified a total of 6 case-control and cohort studies epidemiological studies, published in the last five years, which demonstrated an increased risk of a first coronary event in patients with clinically diagnosed periodontitis or more severe periodontitis compared to patients without periodontitis or less severe periodontitis. Relative risk estimates vary between studies, depending on population characteristics and periodontitis case definitions. There are two cohort studies reporting an association between periodontitis and higher cardiovascular mortality (due to coronary heart disease and cerebrovascular disease).

2.3 | Do people with periodontitis have a higher prevalence of cerebrovascular disease and risk of stroke?

There is evidence from epidemiologic studies for a positive association between periodontitis and cerebrovascular disease. A systematic review (Dietrich et al., 2013), which was updated in preparation for this workshop, identified a total of three case-control and cohort studies, which demonstrate an increased risk of a first cerebrovascular event in patients with clinically diagnosed periodontitis or more

severe periodontitis compared to patients without periodontitis or less severe periodontitis. Relative risk estimates vary between studies, depending on population characteristics and periodontitis case definitions. Furthermore, a recent analysis of data from the ARIC study demonstrated an association between periodontal profile class and incident ischaemic stroke. In this cohort, patients with periodontitis had more than double the risk of cardioembolic and thrombotic stroke compared with periodontally healthy individuals (Sen et al., 2018). In addition, as previously documented, there are two cohort studies reporting an association between periodontitis and higher cardiovascular mortality (due to coronary heart disease and cerebrovascular disease) (Dietrich et al., 2013).

2.4 | Do people with periodontitis have a higher prevalence and incidence of Peripheral Artery Disease (PAD)?

There is limited but consistent evidence that individuals with periodontitis have a higher prevalence and incidence of PAD compared to individuals without periodontitis (Yang et al., 2018). For cross-sectional data, the most significant evidence comes from two large, population-based studies in the United States (NHANES 1999–2002) and South Korea (KoGES-CAVAS). Both studies found a positive association between the extent of clinical attachment loss (NHANES 1999–2002) and severity of radiographic bone loss (KoGES-CAVAS) with PAD, defined using the Ankle Brachial Index (ABI), with adjusted odds ratios (OR) of 2.2 (95% confidence interval [1.2; 2.4]) and 2.0 (95% CI [1.1; 3.9]), respectively (Ahn et al., 2016; Lu, Parker, & Eaton, 2008). One prospective cohort study conducted in male veterans in the United States reported a positive association between periodontitis (measured by severity of radiographic bone loss) and the incidence of PAD over a 25- to 30-year follow-up period, with an adjusted OR of 2.3 (95% CI [1.3; 3.9]) (Mendez et al., 1998). There are no studies that have evaluated the association between periodontitis and the incidence of Major Adverse Limb Events (MALE).

2.5 | Do people with periodontitis have a higher risk of other CVDs or conditions (heart failure, atrial fibrillation)?

Several studies report positive associations between periodontitis and heart failure. There is evidence from a large Asian study using the Taiwanese National Health Insurance Research Database reporting a significantly higher incidence of atrial fibrillation in individuals with periodontal diseases compared to individuals without periodontal diseases (hazard ratio—HR = 1.31, 95% CI [1.25, 1.36]) (Chen, Lin, Chen, & Chen, 2016).

2.6 | Do people with a history of cardiovascular disease have a different incidence or progression of periodontitis?

There is currently limited scientific evidence that CVD is a risk factor for the onset or progression of periodontitis.

2.7 | Do people with periodontitis with history of cardiovascular disease have a higher chance of experiencing a subsequent event?

From three studies investigating the association between periodontitis and secondary cardiovascular events, two large studies did not find a significant association (Dorn et al., 2010; Reichert et al., 2016); however, a small study (100 subjects) reported a significant association (HR = 2.8, 95% CI [1.2; 6.5]) with recurrent cerebrovascular events (Sen et al., 2013).

3 | MECHANISMS THAT MAY EXPLAIN THE EPIDEMIOLOGICAL ASSOCIATIONS BETWEEN PERIODONTITIS AND CVD

3.1 | Is there evidence of a higher incidence of bacteremia following oral function/intervention in periodontitis patients compared to periodontally healthy subjects?

There is evidence that oral bacterial species can enter the circulation and cause bacteremia, which has been demonstrated following daily life activities (toothbrushing, flossing, chewing or biting an apple), although it has been studied more frequently following professional interventions (tooth polishing, scaling, tooth extraction, surgical extraction of third molars and periodontal probing).

The risk of bacteremia has been associated with periodontal health status in a systematic review, suggesting a higher risk of bacteremia associated with gingival inflammation (Tomas, Diz, Tobias, Scully, & Donos, 2012). A recent randomized clinical trial (RCT) concluded that periodontal therapy (by means of scaling and root planing, SRP) induced bacteremia in both gingivitis and periodontitis patients, but the magnitude and frequency were greater among periodontitis patients (Balejo et al., 2017).

Whilst there are methodological limitations in some of the reported studies, the overall picture supports the contention that bacteremia results from daily life activities and oral interventions, and it is more frequent of longer duration and involves more virulent bacteria in periodontitis patients.

3.2 | Is there evidence for the presence of oral bacteria in atheroma lesions?

There is evidence through traces of DNA, RNA or antigens derived from oral bacterial species, mainly periodontal pathogens, that have been identified in atherothrombotic tissues. Studies have attempted to correlate the presence of these bacteria in atherothrombotic tissues, with other sample sources (subgingival plaque, serum, etc.), in the same patients, and these suggest that in periodontitis patients there is a higher probability of a positive correlation (Armingohar, Jørgensen, Kristoffersen, Abesha-Belay, & Olsen, 2014; Mahendra, Mahendra, Felix, & Romanos, 2013). At least two studies have demonstrated viable *P. gingivalis* and *A. actinomycetemcomitans* in atherothrombotic tissue

when culturing the atheroma samples (Kozarov, Dorn, Shelburne, Dunn, & Progulsk-Fox, 2005; Rafferty et al., 2011).

3.3 | Do we have evidence that periodontal bacteria and/or bacterial products and virulence factors influence the pathophysiology of atherosclerosis?

Different animal models have been employed to provide evidence that periodontal pathogens can promote atheroma formation. *P. gingivalis* has been shown to accelerate atherosclerosis in murine models, to induce fatty streaks in the aorta of rabbits and to induce aortic and coronary lesions after bacteremia in normocholesterolaemic pigs (Schenkein & Loos, 2013).

Recently, further evidence has emerged using hyperlipidemic ApoE null mice after infection with *P. gingivalis* and also with a polymicrobial experimental infection (*P. gingivalis*, *Treponema denticola*, *Tannerella forsythia* and *Fusobacterium nucleatum*). A polymicrobial infection was shown to induce aortic toll-like receptor (TLR) and inflammasome signalling, with an enhanced oxidative stress reaction generated within the aortic endothelial cells (Chukkapalli et al., 2015; Velsko et al., 2014, 2015).

There is also *in vitro* evidence of intracellular entry by periodontal pathogens (*P. gingivalis*, *A. actinomycetemcomitans*, etc.) (Reyes et al., 2013). *In vivo* and *in vitro* studies demonstrate the importance of the fimbriae of *P. gingivalis* to host cell entry and to promote atherothrombotic lesions in experimental models (Yang et al., 2014). *In vitro* experiments have shown that certain bacterial strains expressing *P. gingivalis* hemagglutinin A (HagA) have an increased capability to adhere and enter human coronary artery endothelial cells (HCAEC) (Belanger, Kozarov, Song, Whitlock, & Progulsk-Fox, 2012).

3.4 | Do we have evidence that periodontitis patients exhibit increased production and/or levels of inflammatory mediators that also associated with the pathophysiology of atherosclerosis?

There is evidence of significantly higher levels of C-reactive protein (CRP) in periodontitis patients versus healthy controls and in CVD and periodontitis patients compared with either condition alone. The effect of periodontal therapy has been shown to associate with a significant decrease in CRP levels, along with improvements in surrogate measurements of cardiovascular health (Demmer et al., 2013; Koppolu et al., 2013; Patil & Desai, 2013).

There is evidence of elevated levels of serum interleukin (IL)-6 in periodontitis patients and lower levels of IL-4 and IL-18. The effect of periodontal therapy has shown a significant decrease in the serum levels of IL-6, serum amyloid A and alpha 1 anti-chymotrypsin. Peripheral neutrophils from periodontitis patients release excess IL-1 β , IL-8, IL-6 and tumour necrosis factor (TNF)- α when stimulated by periodontal pathogens. Periodontal therapy only partially reduces the cytokine hyper-reactivity with some evidence of a constitutively elevated response (Ling, Chapple, & Matthews, 2016).

3.5 | Do we have evidence that periodontitis patients develop elevations in thrombotic factors that are also associated with the pathophysiology of atherothrombosis?

There is evidence of significantly higher levels of fibrinogen in periodontitis patients versus healthy controls, and in CVD and periodontitis patients compared with either condition alone (Chandy et al., 2017). Periodontal therapy appears to result in a significant decrease in fibrinogen levels (Lopez et al., 2012; Vidal, Cordovil, Figueredo, & Fischer, 2013).

There is evidence from different studies of significantly higher levels of platelet activation markers in periodontitis patients and that these higher levels may be reversed by periodontal therapy (Arvanitidis, Bizzarro, Alvarez Rodriguez, Loos, & Nicu, 2017). However, there is conflicting evidence that significantly higher levels of plasminogen activator inhibitor (PAI) are found in periodontitis patients (Schenkein & Loos, 2003).

3.6 | Do we have evidence that periodontitis patients demonstrate elevated serum antibody levels that cross-react with antigens in cardiovascular tissues?

There is evidence that HSPs from periodontal pathogens (*Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans* and *Fusobacterium nucleatum*) generate antibodies that can cross-react with human HSPs. These antibodies have been shown to activate cytokine production, as well as monocyte and endothelial cell activation.

The presence of anti-cardiolipin antibodies has been significantly associated with periodontitis patients, which reversed following periodontal therapy. There is some evidence that periodontal pathogens can elicit antibodies that cross-react with cardiolipin (Schenkein & Loos, 2003).

In three out of four population-based studies (Parogene study, NHANES III, DANHES), higher levels of serum immunoglobulin (Ig)G against *P. gingivalis* were associated with periodontitis patients and cardiovascular disease (acute coronary syndrome, death from cardiovascular disease and cardiovascular disease). The ATHEROREMO-IVUS study failed to demonstrate an association between serum levels of IgG and IgA against *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythia* and *P. intermedia* and major adverse cardiac events (MACE) (de Boer et al., 2014). This is consistent with data from Boillot et al. (2016).

3.7 | Do we have evidence that periodontitis patients exhibit dyslipidaemia?

There is evidence from systematic reviews that serum total cholesterol levels, low-density lipoproteins (LDL), triglycerides, very-low-density lipoproteins (VLDL), oxidized LDL and phospholipase A2 are elevated in periodontitis. High-density lipoprotein (HDL) levels are reduced in periodontitis patients compared with controls (Schenkein & Loos, 2003). These levels are reversed after periodontal therapy (Teeuw et al., 2014).

3.8 | Do we have evidence for peripheral blood neutrophil hyper-responsiveness in reactive oxygen species and protease production in periodontitis patients?

There is strong mechanistic evidence that peripheral blood neutrophils (PBNs) from periodontitis patients produce higher levels of total and extracellular reactive oxygen species (ROS) than healthy controls, under various conditions of priming and stimulation and from unstimulated cells (Ling et al., 2016; Matthews, Wright, Roberts, Cooper, & Chapple, 2007a). This hyper-reactivity to stimulation by periodontal bacteria is reduced following successful periodontal therapy to control patient levels, but the unstimulated hyperactivity remains, suggesting that constitutive and reactive mechanisms underlie neutrophil hyper-responsiveness in periodontitis (Matthews, Wright, Roberts, Ling-Mountford, et al., 2007b). Gene expression data in PBNs support the functional data (Wright, Matthews, Chapple, Ling-Mountford, & Cooper, 2008). Serum antioxidant levels and those in gingival crevicular fluid (GCF) are reduced in periodontitis patients, reflecting increased ROS activity (Chapple, Brock, Milward, Ling, & Matthews, 2007). These data are supported by a study of endarterectomy samples, which demonstrated evidence for activation of the ROS-generating systems in neutrophils, specifically the presence of myeloperoxidase (MPO), cell-free DNA and DNA-MPO complexes (Range et al., 2014).

3.9 | Are there common genetic risk factors between periodontitis and CVDs?

There is scientific evidence of pleiotropy between periodontitis and cardiovascular diseases (Aarabi et al., 2017; Munz et al., 2018; Schaefer et al., 2015, 2011). The highly pleiotropic genetic locus *CDKN2B-AS1* (chromosome 9, p21.3) associated with coronary artery disease, type 2 diabetes, ischaemic stroke and Alzheimer's disease is also consistently associated with periodontitis (Aarabi et al., 2017; Ernst et al., 2010; Loos, Papantonopoulos, Jepsen, & Laine, 2015; Munz et al., 2018). Its function appears to be related to the regulation of gene expression (Hubbarten et al., 2019). Interestingly, a pilot study identified that a genetic variant in the *CDKN2B-AS1* locus was associated with the extent of elevated levels of C-reactive protein in periodontitis (Teeuw, Laine, Bizzarro, & Loos, 2015).

A conserved non-coding element within *CAMTA1* upstream of *VAMP3*, also first identified as a genetic susceptibility locus for coronary artery disease, was found to be associated with periodontitis (Schaefer et al., 2015). A GWAS suggested that the *VAMP3* locus was associated with a higher probability of subgingival overgrowth of periodontal pathogens (Divaris et al., 2012).

There is evidence for plasminogen (PLG) as a shared genetic risk factor for coronary artery disease and periodontitis (Schaefer et al., 2015).

The 4th pleiotropic locus between coronary artery disease and periodontitis is a haplotype block at the *VAMP8* locus (Munz et al., 2018).

These shared genetic factors suggest a mechanistic link or immunological commonalities between coronary artery disease and periodontitis. The impairment of the regulatory pathways by genetic factors may be a common pathogenic denominator of at least coronary artery disease and periodontitis. There are indications that aberrant inflammatory reactivity, determined by genetic variants in the loci *CDKN2B-AS1* (*ANRIL*), *PLG*, *CAMTA1/VAMP3* and *VAMP8* could partially explain the epidemiological link between periodontitis and cardiovascular diseases.

4 | EVIDENCE FROM INTERVENTION STUDIES

4.1 | Is there an effect of periodontitis treatment in preventing or delaying ACVD events?

4.1.1 | Primary prevention

There have been no prospective randomized controlled periodontal intervention studies on primary prevention of cardiovascular diseases (including first ischaemic events or cardiovascular death) since the last consensus report (Tonetti et al., 2013). The Group questioned the feasibility of performing adequately powered RCTs in primary prevention at a population level due to important ethical, methodological and financial considerations.

However, consistent observational evidence suggests that several oral health interventions including self-performed oral hygiene habits (toothbrushing) (two studies (de Oliveira, Watt, & Hamer, 2010; Park et al., 2019)), dental prophylaxis (one study (Lee, Hu, Chou, & Chu, 2015)), increased self-reported dental visits (one study (Sen et al., 2018)) and periodontal treatment (three studies (Holmlund, Lampa, & Lind, 2017; Lee et al., 2015; Park et al., 2019)) produced a reduction in the incidence of ACVD events.

Cross-sectional data of The Scottish Health Surveys from 1995 to 2003 pertaining 11,869 men and women (mean age of 50 years) were linked to a database of hospital admissions and deaths with follow-up until December 2007 (Information Services Division, Edinburgh) (de Oliveira et al., 2010). Participants who brushed less than once a day exhibited the highest incidence of ACVD events (HR = 1.7, 95% CI [1.3; 2.3]) compared with those who brushed twice a day, indicating that self-performed oral hygiene routines may reduce the incidence of ACVD.

A retrospective nationwide, population-based study in Taiwan, including 511,630 participants with periodontitis and 208,713 controls, used the Longitudinal Health Insurance Database 2000 to estimate the incidence rate of ACVD events from 2000 to 2015 (Lee et al., 2015). The hazard ratio for acute myocardial infarction was reduced more in the group of periodontitis patients who received dental prophylaxis (HR = 0.90, 95% CI [0.86; 0.95]) than intensive treatment (including gingival curettage, scaling and root planing, and/or periodontal flap operation and/or tooth extraction) (HR = 1.09, 95% CI [1.03; 1.15]). Consistent reductions in the incidence rate of ischaemic

stroke were observed in both the dental prophylaxis (HR = 0.78, 95% CI [0.75; 0.91]) and intensive treatment groups (HR = 0.95, 95% CI [0.91; 0.99]).

A cohort of 8,999 patients with periodontitis who received a complete (non-surgical and if needed surgical) periodontal treatment protocol was followed between 1979 and 2012 (Holmlund et al., 2017). During the study follow-up, poor responders to the periodontal treatment had an increased incidence of ACVD events (incidence rate -IR = 1.28, 95% CI [1.07; 1.53]) compared with good responders, suggesting that successful periodontal treatment could reduce the incidence of ACVD events.

In the Atherosclerosis Risk in Communities (ARIC) study including 6,736 participants followed during 15 years, self-reported regular dental care users had a lower risk for ischaemic stroke (HR = 0.77, 95% CI [0.63; 0.94]) compared with episodic care users (Sen et al., 2018).

In a prospective population-based study using data from the National Health Insurance System-National Health Screening Cohort (NHISHEALS) including 247,696 participants free from any CVD history recruited between 2002 and 2003, reported that an increased number of dental caries lesions, the presence of periodontitis and a greater loss of teeth were all associated with an increased risk of future major cardiovascular events (MACEs), including cardiovascular death, acute myocardial infarction, heart failure, and stroke (Park et al., 2019). One additional toothbrushing episode per day was associated with a reduced incidence of ACVD events (HR = 0.91, 95% CI [0.89, 0.93]) and regular professional cleaning reduced the risk even further (HR = 0.86, 95% CI [0.82; 0.90]).

In summary, progression of ACVD may be influenced by successful periodontal treatment independent of traditional CVD risk factor management.

4.1.2 | Secondary prevention

There is only one pilot multicentre study on secondary prevention of ACVD events (PAVE (Couper et al., 2008; Offenbacher et al., 2009)), which reported no statistically significant difference in the rate of CVD events between patients who underwent treatment of periodontitis versus community care (risk ratio -RR = 0.72, 95% CI [0.23; 2.22]). Several methodological limitations highlighted in the trial limit the applicability/usefulness of such evidence to inform the research and healthcare communities.

Thus, there is insufficient evidence to support or refute the potential benefit of the treatment of periodontitis in preventing or delaying ACVD events (Li et al., 2017).

4.2 | What is the effect of the treatment of periodontitis in improving surrogate parameters of CVD?

Table 1 summarizes the evidence on the effect of periodontal therapy on surrogate markers of CVD. There is moderate evidence for reduction of low-grade inflammation as assessed by

serum levels of CRP, IL-6 and improvements in surrogate measures of endothelial function (flow-mediated dilatation of the brachial artery).

Moderate evidence suggests that periodontal treatment does not have an effect on lipid fractions whilst there is limited evidence, suggesting that periodontal treatment reduces arterial blood pressure and stiffness, subclinical ACVD (as assessed by mean carotid intima-media thickness) and insufficient evidence of an effect on ACVD biomarkers of coagulation, endothelial cell activation and oxidative stress.

4.3 | What is the effect of statin intake on clinical periodontal outcomes?

Statins are medications prescribed to decrease LDL cholesterol. Numerous trials have demonstrated their benefit for the prevention of cardiovascular diseases (Yebyo, Aschmann, Kaufmann, & Puhan, 2019).

Interestingly, statins possess various additional properties relevant to the pathogenesis and treatment of periodontitis (Estanislau et al., 2015). In particular, it has been reported that statins are anti-inflammatory (Koh et al., 2002; Paumelle et al., 2006; Quist-Paulsen, 2010; Rosenson, Tangney, & Casey, 1999; Sakoda et al., 2006) can promote bone formation (Garrett, Gutierrez, & Mundy, 2001; Liu et al., 2012; Mundy et al., 1999; Viereck et al., 2005), can inhibit matrix metalloproteinases (MMPs) (Koh et al., 2002; Luan, Chase, & Newby, 2003; Poston et al., 2016) and possess anti-microbial properties (Ting, Whitaker, & Albandar, 2016).

A systematic review with meta-analysis of pre-clinical in vivo trials reported a positive effect of local or systemic statin administration for the prevention of alveolar bone loss in experimental periodontitis models in rodents (Bertl et al., 2018).

Several observational clinical studies have evaluated the effect of systemic statin intake on periodontal conditions (Lindy, Suomalainen, Mäkelä, & Lindy, 2008; Meisel, Kroemer, Nauck, Holtfreter, & Kocher, 2014; Sangwan, Tewari, Singh, Sharma, & Narula, 2013; Saver, Hujoel, Cunha-Cruz, & Maupome, 2007; Saxlin, Suominen-Taipale, Knuuttila, Alha, & Ylostalo, 2009; Subramanian et al., 2013). Statin use was not found to be associated with decreased tooth loss in adults with chronic periodontitis when analysing administrative health plan data (Saver et al., 2007). However, a 5-year population-based follow-up study comparing participants treated with statins with those who did not medicate with statins concluded that long-term treatment with statins was associated with reduced tooth loss (Meisel et al., 2014). Furthermore, patients on statin medication were reported to exhibit significantly fewer signs of periodontal inflammatory lesions than patients without a statin regimen (Lindy et al., 2008). A cross-sectional study compared the periodontal status of patients with hyperlipidaemia (with or without statin intake) to normolipidaemic individuals and found higher gingival bleeding and probing depths in the hyperlipidaemic patients who were not statin users (Sangwan et al., 2013). In a RCT, periodontal patients with risk factors or with established atherosclerosis were assigned to either high- or low-dose statin intake (Subramanian et al., 2013). After 3

TABLE 1 Summary of the evidence on the effect of periodontal therapy on surrogate markers of cardiovascular diseases

Topic	Outcome	Number of RCTs and SR since last consensus	References	Effect	Overall Level of Evidence
Effect of Periodontal Therapy on Lipids	Lipids (multiple)	6 RCTs	Caula, Lira-Junior, Tinoco, and Fischer (2014); D'Aiuto et al. (2018); Deepti, Tewari, Narula, Singhal, and Sharma (2017); Fu, Li, Xu, Gong, and Yang (2016); Hada, Garg, Ramteke, and Ratre (2015); Kapellas et al. (2014)	No	Moderate
Effect of Periodontal Therapy on Blood Pressure	Systolic, diastolic	3 RCTs	D'Aiuto et al. (2018); Hada et al. (2015); Zhou et al. (2017)	Yes	Limited
Effect of Periodontal Therapy on Endothelial Function	Endothelial Function (multiple measures)	2 RCTs 1 SR	D'Aiuto et al. (2018); Saffi et al. (2018) Steffel et al. (2018b)	Yes	Moderate
Effect of Periodontal Therapy on interleukin (IL)-6	IL-6	3 RCTs	Fu et al. (2016); Kapellas et al. (2014); Zhou et al. (2017)	Yes	Moderate
Effect of Periodontal Therapy on C-Reactive Protein (CRP)	CRP	5 SR 7 RCTs following 2014	Demmer et al. (2013); Freitas et al. (2012); Ioannidou, Malekzadeh, and Dongari-Bagtzoglou (2006); Paraskevas, Huizinga, and Loos (2008); Teeuw et al. (2014) D'Aiuto et al. (2018); Deepti et al. (2017); Kaushal, Singh, Lal, Das, and Mahdi (2019); Caula et al. (2014); Hada et al. (2015); Kapellas et al. (2014); Zhou et al. (2017)	Yes	Moderate
Effect of Periodontal Therapy on Pulse Wave Velocity (PWV)	PWV	1 RCT	Kapellas et al. (2014)	No	Limited
Effect of Periodontal Therapy on carotid intima-media thickness (cIMT)	Common cIMT	1 RCT	Kapellas et al. (2014)	Yes	Limited

Abbreviation: RCT, randomized clinical trial; SR, systematic review.

months, a significant reduction of periodontal inflammation was seen in the high-dose compared to the low-dose group. Thus, within the limits of the above-reported studies, there is some limited evidence, suggesting that statins may have a positive impact on periodontal health.

Very few clinical studies have been designed to evaluate the effect of adjunctive systemic statin intake in conjunction with periodontal therapy (Fajardo, Rocha, Sanchez-Marin, & Espinosa-Chavez, 2010; Fentoglu et al., 2012; Sangwan, Tewari, Singh, Sharma, & Narula, 2016). In a randomized placebo-controlled pilot study in 38 patients with chronic periodontitis, adjunctive statin intake led to beneficial effects on radiological bone loss and tooth mobility after 3 months (Fajardo et al., 2010). Another 3-month study compared the treatment response to nonsurgical periodontal therapy in 107 chronic periodontitis patients (35 normolipidaemic as control, 36 hyperlipidaemic on non-pharmacological therapy and 36 hyperlipidaemic on statins) and found a greater improvement in gingival index in the normolipidaemic control and in the statin groups (Sangwan et al., 2016). Based on this limited evidence, two recent systematic reviews with meta-analysis on the effects of (local and systemic) statins on periodontal treatment concluded that systemic statin intake does not enhance the outcomes of periodontal therapy (Bertl et al., 2017; Muniz et al., 2018).

5 | CARDIOVASCULAR RISKS AND COMPLICATIONS OF PERIODONTAL THERAPEUTIC INTERVENTIONS

5.1 | Is there an ischaemic cardiovascular risk for patients undergoing periodontal therapy?

Non-surgical treatment of periodontitis involving supra- and subgingival instrumentation of the affected dentition (under local anaesthesia) is often delivered in several short sessions. Alternatively, full-mouth non-surgical periodontal treatment can be performed within 24 hours.

Delivering periodontal treatment in a full-mouth fashion (i.e. within 24 hours) triggers a one-week acute systemic inflammatory response associated with transient impairment of endothelial function (Orlandi et al., 2019). This distant effect is not observed when periodontal treatment is delivered across several separate sessions (Graziani et al., 2015). This is achieved by limiting the number of teeth involved and the time devoted to completing the dental instrumentation. These findings raise the question of whether performing longer sessions of periodontal treatment could contribute to an individuals' inflammatory burden/risk and increase their short-term risk of suffering from a vascular event.

There is consistent and strong observational evidence that common acute infections/inflammatory responses are associated at a population level with an increased risk of vascular events within the first 4 weeks of the infectious/inflammatory event (Smeeth et al., 2004).

5.1.1 | At population level

There is no evidence for specific effects of periodontal treatment procedures on increasing ischaemic cardiovascular risk. Two observational studies reported no effect of “*invasive dental treatment*” in elevating ischaemic cardiovascular risk (Chen et al., 2019; Nordendahl et al., 2018), and one study suggested a minimal increased risk within 4 weeks following treatment (Minassian, D’Aiuto, Hingorani, & Smeeth, 2010).

Chen et al. (2019) performed a case-crossover and self-controlled case series using the Taiwanese National Health Insurance Research Database, including over 110,000 Myocardial Infarction cases and 290,000 ischaemic stroke patients between 1999 and 2014. They reported a non-significant increase in the incidence of myocardial infarction within the first 24 weeks following “*invasive dental treatment*” (including periodontal procedures) except for a modest risk of myocardial infarction during the first week for patients without other comorbidities (OR = 1.31, 95% CI [1.08; 1.58], after 3 days).

A registry-based case-control study between 2011 and 2013 including 51,880 cases who underwent an “*invasive dental procedure*” compared to 246,978 controls reported no association with an increased incidence of myocardial infarction (OR 0.98, 95% CI [0.91; 1.06]) (Nordendahl et al., 2018).

Minassian et al. (2010) performed a self-controlled case series including nearly 10 million participants included in an insurance database from 2002 and 2006 in the United States. The analysis showed that *invasive dental treatment* (largely comprising of tooth extractions and only 4% being non-surgical and surgical periodontal procedures) is associated with an increased risk of incident acute cardiovascular events (IR = 1.5, 95% CI [1.09; 2.06]) within the first 4 weeks of treatment recorded.

In summary, the Group concluded that delivering periodontal treatment is safe with regard to cardiovascular risk.

5.1.2 | In patients with established CVD

There is limited evidence on the effects of “*invasive dental treatment*” on the incidence of ischaemic events in patients with established CVD or after an event.

A small RCT on the effects of the treatment of periodontitis on CVD biomarkers in patients with established CVD (Montenegro et al., 2019) showed no cardiovascular adverse events within 3 months of completion of scaling and root planing (periodontal therapy).

In the PAVE feasibility randomized secondary prevention trial, provision of periodontal scaling and root planing treatment in patients with established CVD did not increase the incidence of cardiovascular events compared to the control group (community treatment) within 6 months (Beck et al., 2008).

In summary, the Group concluded that delivering periodontal treatment is safe with regard to cardiovascular risk in patients with established CVD.

5.2 | What is the perioperative bleeding risk when performing periodontal therapy?

Periodontal treatment consists of numerous procedures with different levels of bleeding risk. This risk of bleeding is however low in the vast majority of procedures, and it can be easily controlled with local haemostatic measures.

Perioperative bleeding risk varies according to the extent and invasiveness of the periodontal procedure performed. The majority of periodontal procedures may be grouped within the ESC/AHA/EHRA (Steffel et al., 2018a, 2018b). Low bleeding risk group (frequency less than 1% of post-operative bleeding) group: supragingival polishing, non-surgical periodontal treatment, conventional surgical periodontal treatment (conservative, resective or regenerative), tooth extractions and dental implant placement. Moderate bleeding risk (frequency between 2 and 5%) may be observed in major autogenous bone augmentation procedures such as block bone harvesting, sinus floor elevation and procedures where healing is by secondary intention, such as free gingival grafting. Appendix S1 summarized the main recommendations for patients with antithrombotic therapy when performing periodontal therapy.

5.2.1 | In patients undergoing antiplatelet therapy

Individuals undergoing single acetylsalicylic acid (ASA) therapy (aspirin) in different therapeutic dosages, as well as therapy with clopidogrel, ticlopidine or ticagrelor, show no statistically significant differences in frequency of bleeding events when compared to controls, that is subjects not undergoing antiplatelet therapy (Doganay, Atalay, Karadag, Aga, & Tugrul, 2018; Lillis, Ziakas, Koskinas, Tsirlis, & Giannoglou, 2011).

Dual antiplatelet therapy, most commonly ASA in combination with clopidogrel, may pose a certain risk for post-operative bleeding complications; however, it appears that these haemorrhagic events may be managed safely with local haemostatic measures (Napenas et al., 2009; Nathwani & Martin, 2016).

Thus, current evidence does not support discontinuation of antiplatelet therapy before dental procedures, irrespective of the type of therapy employed (single or dual antiplatelet therapy) or the type of procedure performed (single, multiple tooth extractions, non-surgical and surgical periodontal therapy and dental implant procedures).

5.2.2 | In patients undergoing anticoagulant therapy

Vitamin K antagonists

In patients taking oral anticoagulant therapy (vitamin K antagonists, VKA) and undergoing dental extraction, minor dental procedures

and dental implant placement do not seem to increase the risk of bleeding compared to patients who discontinue oral anticoagulant therapy (Shi, Xu, Zhang, Zhang, & Liu, 2017; Yang, Shi, Liu, Li, & Xu, 2016). There may be a higher post-operative bleeding risk in patients continuing VKA and undergoing either minor dental surgery or other higher-risk procedures when compared to non-VKA patients (Biedermann et al., 2017; Shi et al., 2017), but local haemostatic agents appear to be effective in controlling post-operative bleeding (Madrid & Sanz, 2009).

Novel/direct anticoagulants (DOAC/NOAC)

Limited trials and evidence are available on the management of patients on novel oral anticoagulant (NOAC) therapy undergoing dental treatment; hence, the Group concluded that further studies regarding dental procedures in these patients are strongly encouraged.

It appears there is no need for interruption of NOAC therapy in most dental treatments, due to a low incidence of bleeding complications, which can be successfully managed with local haemostatic measures when comparing groups continuing NOAC and groups discontinuing NOAC therapy (Kwak et al., 2019; Lababidi et al., 2018; Patel et al., 2017; Yagyuu et al., 2017) and with reported timing of discontinuation and reinstatement varying greatly. When comparing NOAC patients with healthy individuals, there seems to be a higher incidence of delayed bleeding (2 days and later) in those patients who do not discontinue NOAC therapy (Miclote et al., 2017).

6 | RECOMMENDATIONS

6.1 | Recommendations for oral health professionals for use in dental practice/office for people with cardiovascular disease (CVD)

- Patients with periodontitis should be advised that there is a higher risk for cardiovascular diseases, such as myocardial infarction or stroke, and as such, they should actively manage all their cardiovascular risk factors (smoking, exercise, excess weight, blood pressure, lipid and glucose management, and sufficient periodontal therapy and periodontal maintenance).
- Patients with periodontitis and a diagnosis of CVD should be informed that they may be at higher risk for subsequent CVD complications, and therefore, they should regularly adhere to the recommended dental therapeutic, maintenance and preventive regimes.
- Patients collect a careful history to assess for CVD risk factors, such as diabetes, obesity, smoking, hypertension, hyperlipidaemia and hyperglycaemia. Patients suggest that the patient consults his/her physician if any of these risk factors are not appropriately controlled.
- Oral health education should be provided to all patients with periodontitis and a tailored oral hygiene regime, including twice-daily

brushing, interdental cleaning and, in some cases, the use of adjunctive chemical plaque control, may be appropriate.

- People presenting with a diagnosis of CVD should receive a thorough oral examination, which embeds a comprehensive periodontal evaluation, including full-mouth probing and bleeding scores.
- If no periodontitis is diagnosed initially, patients with CVD should be placed on a preventive care regime and monitored regularly (at least once a year) for changes in periodontal status.
- In people with CVD, if periodontitis is diagnosed, they should be managed as soon as their cardiovascular status permits.
 - o Irrespective of the level of CVD or specific medication, non-surgical periodontal therapy should be provided, preferably in several 30- to 45-min sessions, in order to minimize a spike of acute systemic inflammation
 - o Surgical periodontal and implant therapy when indicated should be provided in a similar manner as in patients without CVD.

However, attention should be paid to:

- Hypertension. It is recommended to measure the patients' blood pressure (after appropriate relaxation) before the surgical intervention, and in cases of high blood pressure (above 180/100 according to expert opinion), the surgery should be postponed until the patient's blood pressure is stabilized.
- Medication with antiplatelet and anticoagulant drugs. Since periodontal and implant surgical procedures usually impart only a low-to-medium risk of bleeding in general terms, the dentist should not change a patient's medication, or in cases of doubt, he/she should consult the physician/cardiologist prior to the surgical intervention. Consideration should also be given to the local management of bleeding complications that may arise.

Current AHA/ACC/SCAI/ACS/ADA/ESC/ACCP guidelines on perioperative management of antithrombotic therapy do not suggest discontinuation of anti-platelet therapy for low bleeding risk procedures (Douketis et al., 2012; Grines, Bonow, & Casey, 2007; Kristensen et al., 2014).

Various approaches for peri-operative management of anticoagulant therapy have been suggested. The Group reviewed the guidelines on perioperative management of vitamin K antagonists (VKA) and suggested discontinuation of medication treatment if the INR is 4 or below for low or medium bleeding risk procedures (Perry, Noakes, Helliwell, & British Dental, 2007). However, if the INR (internationalized normalized ratio) is 3.5 or above, the expert group recommends that dental clinicians seek advice and consult with the responsible medical professional. Management of high thromboembolic risk cases should be collaborative in consultation with the medical professional responsible for VKA therapy (Kristensen et al., 2014; Valgimigli et al., 2018).

After reviewing novel anticoagulant (non-VKA) and direct anticoagulant (NOAC/DOAC) therapies guidelines, the Group concluded that for low bleeding risk periodontal procedures no discontinuation of anticoagulants is recommended (Steffel et al., 2018a, 2018b). These

procedures could be performed 18–24 hrs after the last intake (depending on a renal function assessment for the medication in question) and then restart 6 hrs following treatment. The expert group, however, strongly recommends that the dental clinician should consult with the responsible medical professional. When a medium bleeding risk periodontal procedure is planned, discontinuation of therapy should be agreed with the medical professional responsible for and/or prescribing the anticoagulant therapy.

Lastly, in cases of combined antiplatelet and anticoagulant therapies that pertain patients with the highest thrombotic and ischaemic risk (i.e. chronic atrial fibrillation or after an acute myocardial infarction or recent coronary stenting), when periodontal procedures (either of low or medium bleeding risk) are required, any alterations in medication should be discussed and agreed upon with the responsible medical professional (Steffel et al., 2018a, 2018b). In elective periodontal procedures, the operation should be delayed until after treatment stabilization and appropriate consultation with the medical specialist.

In cases of triple therapy (dual antiplatelet and one anticoagulant) or one anticoagulant plus one antiplatelet, such patients need individualized management by the responsible medical professional according to their thrombotic and haemorrhagic risk (Valgimigli et al., 2018).

It is important to highlight that local haemostatic agents (such as oxidized cellulose, absorbable gelatin sponges, sutures, tranexamic acid mouthwashes, compressive gauze soaked in tranexamic acid) should be used and dental clinicians should consider the confounding effect of local anaesthetic with vasoconstrictors.

- Patients with a risk of endocarditis should be premedicated with antibiotics following current guidelines (such as the European or the American guidelines).
- People with cardiovascular disease who have extensive tooth loss should be encouraged to pursue dental rehabilitation to restore adequate mastication for proper nutrition.

People without a diagnosis of CVD, but with risk factors for CVD should be informed about their CVD risk and referred to a physician for appropriate risk assessment, diagnostic testing and follow-up care. For oral health professionals, risk assessment may be performed based upon the recommendations of the *European Society of Cardiology (Systematic COronary Risk Evaluation, SCORE)* (Sixth Joint Task Force of the European Society of Cardiology & Other Societies on Cardiovascular Disease Prevention in Clinical Practice, 2016).

6.2 | Recommendations for physicians and other medical health professions for use in cardiology practice

Because of the potential negative impact of periodontitis on CVD complications, the following recommendations are made:

- Patients with CVD should be advised that periodontitis may have a negative impact on CVD and may also increase the risk of CVD events.

- Patients should be advised that effective periodontal therapy may have a positive impact upon CV health.
- For people with CVD, physicians should ask about a prior diagnosis of periodontitis. If a positive diagnosis has been made, the physician should seek to ascertain that appropriate periodontal care and maintenance are being provided.
- Patients with CVD should be asked about any signs and symptoms of periodontitis, including bleeding gums during brushing or eating, loose teeth, spacing or spreading/drift of the teeth, oral malodor and/or abscesses of the gums or gingival suppuration.
 - If a positive history is elicited, then a prompt periodontal evaluation should be recommended before their scheduled annual check-up.
 - In the case of a negative history, people with CVD should be advised to check for the above symptoms, and if a positive sign appears, they should visit their dentist at least once per year.
- For all patients with newly diagnosed CVD, referral for a periodontal examination should occur as part of their ongoing management of CVD. Even if no periodontitis is diagnosed initially, an annual oral/dental check-up is recommended.
- The physician should liaise with the dental surgeon over periodontitis management in CVD patients on anticoagulant/antiplatelet therapy prior to the oral intervention and/or periodontal surgery, to avoid excess bleeding or the risk of ischaemic events.

6.3 | Recommendations for patients at the dental surgery/ office who have CVD or are found to be at risk of CVD

- People with CVD must be aware that gum disease is a chronic condition, which may aggravate their CVD and requires lifelong attention and professional care.
- There is a need to clean the teeth and gums very carefully at home. Personalized advice will be provided by the oral health professional.

This may include the following:

- Twice-daily brushing with either a manual or electric toothbrush;
- Cleaning between teeth using interdental brushes where they fit, and where they do not fit, then flossing may be useful;
- Use of specific dentifrices and/or mouth rinses with proven activity against dental plaque, if advised by oral health professionals;
- If left untreated, gum disease can lead to tooth loss and may also make CVD preventive measures harder to control;
- Gum disease may be present and deteriorate with no apparent symptoms, so the dentist should advise their patient that even without current gum disease, they should still receive regular dental check-ups as part of managing their CVD.

Dentists should be able to identify the early signs of gum disease, but patients should also suspect gum disease if noticing:

- Red or swollen gums;
- Bleeding from the gums or blood in the sink after toothbrushing;
- Foul taste;
- Longer looking teeth;
- Loose teeth;
- Increasing spaces between teeth/ teeth moving apart;
- Calculus (tartar) on teeth.

Patients should inform their dentist about the outcome of their visits to the physician and provide an update on their CVD history and any changes in medications. Patients should inform the dentist if they are on anticoagulant therapy.

Patients should understand that it is important to keep their mouth and whole body as healthy as possible with regular dental and medical visits.

6.4 | Recommendations for patients with CVD at the physician's practice/office

6.4.1 | Why should I have my gums checked?

If your physician has told you that you have cardiovascular disease (CVD), you should make an appointment with a dental surgeon to have your mouth and gums checked.

This is because people with CVD may have a higher chance of getting further complications when they have gum disease. The earlier you seek help, the better the outcome will be.

6.4.2 | What should I look for that may tell me I have problems with my gums?

You may have gum disease if you have ever noticed:

- Red or swollen gums;
- Bleeding from your gums or blood in the sink after you brush your teeth;
- Foul taste;
- Longer looking teeth;
- Loose teeth;
- Increasing spaces between your teeth, or your teeth drifting apart;
- Calculus (tartar) on your teeth.

If you have noticed any of these problems, it is important to see a dentist as soon as possible.

6.4.3 | Can I have gum disease without these signs being present?

Gum disease may also be present and get worse with no apparent signs to you that you have it, especially if you smoke, so even if you do not think you have gum disease now, you should still have annual check-ups of your mouth as part of managing your CVD. Your dentist will be able to pick up early signs of gum disease.

6.4.4 | What can I do to prevent gum disease?

You need to clean your teeth and gums twice daily at home for a minimum of 2 min. Also, cleaning between your teeth daily is important and your oral health professional will show you how to do this. You should visit a dental surgeon as soon as possible for a diagnosis and advice on what you need to do. It is important to keep your mouth as healthy as possible with regular oral and dental care, according to the recommendations of your oral health professional.

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ANTITHROMBOTIC THERAPY: WHEN, HOW AND WHY. COMPREHENSIVE APPROACH FOR ORAL HEALTH PROFESSIONALS

Introduction

The use of antithrombotic therapy is one of the cornerstones of cardiovascular medicine, as the main pathophysiological event is thrombus formation. The widespread use of antithrombotic agents is an indisputable fact and is increasing everyday with the ageing of the general population and the unstoppable growth of cardiovascular diseases (CVD) prevalence. Altogether, the number of available agents, indications and timing of these therapeutic interventions is a matter of constant discussion and controversy. This document pretends to complement the current recommendations of the Joint Committee of the European Federation for Periodontology (EFP) and the World Heart Federation (WHF) with an overview of the rationale of the antiplatelet and anticoagulant therapies in the setting of cardiovascular disease, to increase awareness of the dos and don'ts of these medications and optimize the thrombotic and bleeding of patients with CVD that undergo periodontal interventions.

Pharmacology of antithrombotic agents

Thrombus prevention is based on the interruption of the haemostasis, and this can be achieved by intervening in the primary haemostasis (namely, platelet function) or secondary haemostasis (basically, humoral factors). Agents whose main target is primary haemostasis are usually called antiplatelet drugs and are widely used in circumstances in which the main phenomenon is local thrombosis (e.g. myocardial infarction, non-embolic strokes, etc.). On the other hand, drugs that alter secondary haemostasis are generally referred to as anticoagulants and are used in conditions that increase the risk of clot formation with subsequent embolization (e.g. atrial fibrillation, deep vein thrombosis, etc.).

Antiplatelet drugs

The currently commercialized antiplatelet drugs of common use are:

- Acetylsalicylic acid (ASA - Adiro[®])
- AntiP2Y12: usually, these medications are used as adjuvants in situations of abnormally high thrombotic risk, such as the months after a myocardial infarction (MI) or the placement of a coronary stent. When compared with ASA, all of these drugs have a higher antithrombotic power and, thus, a higher bleeding risk. That is why it is of no surprise that, when used as adjuvants therapies together with ASA, the final risk of bleeding arises from a synergistic effect of both drugs and is markedly elevated compared with single antiplatelet therapy. As the thrombotic risk in the aforementioned situations (recent MI, recent coronary stent placement) decreases with time, the use of these agents is almost always limited for a number of months after the event. These group includes:

- o Clopidogrel (Plavix[®])
- o Ticagrelor (Brilique[®], Brilinta[®], Ticalog[®])
- o Prasugrel (Efient[®], Effient[®], Agrepres[®], Prasugil[®], Prasita[®])

The last two agents, namely ticagrelor and prasugrel, were released several years after the commercialization of clopidogrel due to some concerns regarding the efficacy of the latter in selected populations with resistance its biological effect. Both medications have shown a higher platelet inhibition when compared to clopidogrel with a logically expected increase in the bleeding rates. No studies have addressed the comparative risk of ticagrelor against prasugrel.

There are other available antiplatelet drugs, but their use is restricted to very specific and rarely situations that are beyond of the scope of this review and, thus, would not be review.

Anticoagulant drugs

The span of anticoagulant drugs is broader, as it included both oral and parenteral families. The oral anticoagulant medications include:

- Vitamin K antagonists (VKA): These anticoagulants were the first oral agents in the market and have been available for more than 20 years. Their use is widely extended, as they are very cheap agents and the medical community is very comfortable with its use. Another positive feature is that the dose can be titrated to achieve higher or lower anticoagulant effect, depending on the thrombotic risk of the patient. However, they have some setbacks that are to be considered. Firstly, the dose is not predictable, so the patient must routinely undergo haemostasis checks at least monthly to adjust the dosage regime. In addition, these agents are tightly bound to plasmatic proteins and tend to interact with medications that displace them from that union (e.g. non-steroidal anti-inflammatory drugs, antibiotics, etc.). Also, their effect varies widely with vitamin K intake with the diet. All in all, these medications can be quite uncomfortable for both the patient and the doctor: the patient has to be disciplined with the diet and the dosage regime, and should be aware of all the medications that can interact. Physicians, on the other hand, have to check these patients up monthly to adjust the dose. The active principles of this group are:

- o Warfarin (Coumadin[®], Farin[®], Aldocumar[®])
- o Acenocumarol (Sintrom[®])

While in North America the use of warfarin is much more frequent, acenocumarol is the preferred choice in Europe.

- Direct Oral Anticoagulants (DOACs): this group encompasses four different drugs divided into direct thrombin inhibitors and Xa factor inhibitors. The benefits these medications have in comparison with VKA is that their dose is predictable, so no dose monitoring is necessary. Also, their interactions are limited and much more infrequent. Regarding outcomes, these drugs have shown to be at least non-inferior to acenocumarol in embolic prevention with a better safety profile as measured by a lower bleeding risk.

This better overall profile is the reason why DOACs are now the first line therapy with patients with atrial fibrillation (AF) according to the current clinical practice guidelines. However, not all the AF patients are candidates for these medications. This group includes:

- o Dabigatran (Pradaxa[®]): available as 110 mg or 150 mg tablets. It is used twice a day.
- o Rivaroxaban (Xarelto[®]): available as 15 mg or 20 mg tablets. It is used once daily.
- o Apixaban (Eliquis[®]): available as 2.5 mg or 5 mg tablets. It is used twice a day.
- o Edoxaban (Lixiana[®]): available as 30 mg or 60 mg tablets. It is used once daily.

Other than the above, sometimes patients can be on parenteral anticoagulant therapies such as low molecular weight heparins. These medications are normally used during short periods of time while bridging in between drugs.

Indications

For single antiplatelet therapy (SAPT)

Every patient with any form of CVD that belong to the atherosclerotic spectrum (coronary artery disease, cerebrovascular disease or peripheral artery disease) should start indefinite treatment with an antiplatelet agent. For this indication, the most extended practice is to use ASA, but also clopidogrel can be used. Ticagrelor and prasugrel are never used in monotherapy (Neumann et al., 2008; Task Force Members et al., 2018).

Although this has been widely discussed during several decades, the use of ASA in primary prevention is currently not justified and should be avoided.

Other than the above, there are several conditions that also require the utilization of ASA, such as some cases of antiphospholipid syndrome or the presence of intracardiac structural devices (mitral clip, atrial and/or ventricular septal defect occluders, bioprosthetic valves, etc.)

For double antiplatelet therapy (DAPT)

- Coronary artery disease (CAD): patients with CAD require DAPT in the following situations (Ibanez et al., 2014; Neumann et al., 2008):
 - o Chronic angina pectoris: after the implantation of a coronary stent, it is generally recommended to use DAPT for 6 months, after which the patient can discontinue the second antiplatelet drug and stay only on ASA. In some cases of high risk of bleeding, the duration can be shortened to three months. The only combination approved for this scenario is ASA + clopidogrel.
 - o Acute coronary syndrome (myocardial infarction): after a myocardial infarction, it is recommended to use DAPT for a duration of 12 months. However, in some cases, the duration

can be shortened to only one month, after which the patient should discontinue the second agent and remain on ASA indefinitely. First month after stent implantation is particularly critical, so no patient should suspend DAPT within this time window. Preferably, the patient should be on ASA + ticagrelor/prasugrel, but ASA + clopidogrel is also acceptable if there are contraindications for the other agents.

- Cerebrovascular disease (CeVD): patients with CeVD require DAPT in the following situations:
 - o Chronic carotid disease: in symptomatic patients with carotid stenosis that undergo carotid stenting, ASA + clopidogrel is recommended for one month. After that, the patient can discontinue one of the two agents and remain indefinitely on the other (usually clopidogrel is discontinued).
 - o Acute ischemic stroke: the use of DAPT for secondary prevention of stroke has not shown consistent positive results in this scenario. Thus, it is not routinely recommended.
- Peripheral artery disease (PAD) (European Stroke Organisation et al., 2012):
 - o Chronic lower extremity artery disease: in symptomatic patients that undergo lower limb percutaneous revascularization (stenting), ASA + clopidogrel is recommended for one month. After that, the patient can discontinue one of the two agents and remain indefinitely on the other (usually clopidogrel is discontinued).
 - o Acute ischemic lower limb event: the use of DAPT for secondary prevention of lower limb occlusions has not shown consistent positive results in this scenario. Thus, it is not routinely recommended.

Chronic Oral Anticoagulation (COA)

There are three main indications for anticoagulation:

- Deep vein thrombosis (DVT) and pulmonary embolism (PE) (Konstantinides et al., 2019): both VKA and DOACs are authorized for this indication. The duration of the therapy depends on whether it is assumed to be a spontaneous case (3–6 months) or secondary to a non-solvable condition (may even be indefinite). When using VKA, the optimal international normalized ratio (INR) range is 2 to 3.
- Atrial arrhythmias with high risk of systemic embolism (AF, Atrial Flutter): the indication for chronic anticoagulation in the setting of AF/AFlutter is guided by the risk of embolism. Although the method for the risk estimation varies worldwide, European Society of Cardiology (ESC) guidelines recommend the use of CHADSVASc scale. Generally, it is accepted that the following patients with a score equal to 2 or higher must use chronic oral anticoagulant therapy. For this indication, again, both VKA and DOAC can be used, being the latter the first line therapy. When using VKA, the optimal INR range is 2 to 3.
- Valve heart diseases with high risk of systemic embolism: this situation includes significant mitral stenosis and mechanical valve

prosthesis. Tissue valves are not at a high risk of systemic embolism. These situations are the ones with the highest thrombotic risk in the whole area of cardiovascular medicine. As the “power” of the anticoagulation with DOACs was proven to be insufficient in these patients and entailed an increased thrombotic risk, VKA are the only option. In the case of mitral mechanical prosthesis, the optimal INR range is 2.5–3.5, while aortic valve prosthesis can be handled between 2–3. However, some older prosthetic models are known to be more thrombogenic than newer ones and could require INR of up to 4.

Combined Therapies: SAPT/DAPT with COA

Usually, patients with indication for chronic SAPT with either ASA or clopidogrel and indication for COA are encouraged to take COA alone. This strategy has been assessed in several studies and proved to be safe from a secondary prevention point of view, with a reduced risk of bleeding when compared with concomitant SAPT and COA.

On the other hand, the management of patients with indication for DAPT and COA is normally seen in patients that are undergoing coronary stent implantation and have either atrial arrhythmias (more frequent) or mitral stenosis/mechanical valves (less frequent). Depending on the bleeding risk of the patients, two different approaches can be chosen:

- Normal bleeding risk: short period of triple therapy (1-3 months of DAPT+COA) and a transition period with SAPT and COA (3-12 months). After that, it is recommended to downgrade to simple COA therapy.
- High bleeding risk: the short period is either reduced to 1 month or omitted, leaving the patient on SAPT+COA for a minimum of 12 months.

Treatment withdrawal: safety and rationale

It is not the purpose of this paper to give recommendations on timing and indications of withdrawal, but rather explain the changes/effects that the antithrombotic withdrawal entails.

Risks of antiplatelet withdrawal

The main risk of SAPT withdrawal is, of course, the increase in thrombotic risk as explained by a higher chance of MI, stroke or peripheral artery thrombosis. It should be noticed that patients with implanted stents are at a much greater risk of acute events after SAPT withdrawal.

Regarding DAPT, the crucial thing to be understood is that whenever DAPT is used, an abnormally high thrombotic risk underlies. The duration of DAPT regimes depends on several factors, but there should be always a preestablished goal (e.g. 6 months, 12 months, etc.). Transitioning from DAPT to SAPT before the preestablished goal should always be performed under cardiological supervision. Specially, the first month after a coronary stent implantation is of

vital importance, as discontinuation of antiplatelet therapy can easily lead to stent thrombosis, a complication that could be fatal.

After discontinuing an antiplatelet agent, the effect does not wear off immediately:

- ASA: 10 days until absence of effect.
- Clopidogrel: 3 days for significant decrease in effect. 5 days for absence of effect.
- Ticagrelor: 3 days for significant decrease in effect. 5 days for absence of effect.
- Prasugrel: 5 days for significant decrease in effect. 7 days for absence of effect.

Risks of anticoagulation withdrawal

Patients with indication for COA that stop taking these medications are at an increased risk for thromboembolic complications. The overall risk of the thrombotic complications highly depends on the indication for COA.

In patients with mitral stenosis or mechanical heart valves, the discontinuation of VKA leads to an extremely thrombotic risk, specially for patients with mechanical valves in mitral position. Thus, discontinuation of this therapy in such patients should always be supervised by cardiovascular professionals and usually requires bridging treatment with heparin (Baumgartner et al., 2008).

On the counterpart, patients without those conditions, can normally be off DOAC/VKA for brief periods of time with an assumable thromboembolic risk, specially in patients with CHADSVASc scores between 2-6. However, discontinuation of VKA is not recommended anymore for procedures other than those with high bleeding risk. After an oral cavity intervention with significant bleeding, DOACs can be safely restarted 24 hours later.

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