Episode 81 – Cardiovascular Disease – Part 3: Oral Health

March 31, 2023

Cardiovascular disease and oral health

Based on research conducted over several decades, oral health is increasingly recognized as an important factor in cardiovascular health. Periodontitis and cardiovascular disease (CVD) share risk factors, such as tobacco use, obesity, poor nutrition, and physical inactivity. Although causal relationships have not yet been established, research has linked various oral health issues with an elevated risk of CVD, including hypertension, carotid atherosclerosis, and myocardial infarction.[1] [1] [2] [3] [4]

Hypertension

Hypertension is the leading preventable risk factor for CVD and all-cause mortality worldwide. In 2010, 31% of the global adult population (1.4 billion people) had hypertension. This number is expected to greatly exceed 1.6 billion in 2025. Prevalence of hypertension is rising globally owing to an aging population and increases in lifestyle risk factors, such as tobacco use, unhealthy diets (e.g., high sodium and low potassium intake), and low physical activity. [5] [6]

Although hypertension does not typically cause symptoms, long-term hypertension is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Since hypertension is a major risk factor for morbidity and mortality associated with CVD, its prevention and treatment are important. Many studies have reported a link between hypertension and oral health. [7] [8]

Tada et al. (2022) conducted a systematic review and meta-analysis on the association between tooth loss[2] and hypertension. Hypertension was defined as blood pressure chronically 140/90 mmHg or higher. The study included 20 cross-sectional and four cohort studies. Meta-analyses revealed a statistically significant association between tooth loss and hypertension. The authors found individuals with fewer remaining teeth exhibited higher prevalence and incidence of hypertension. Those with more tooth loss had significantly higher systolic blood pressure, but not diastolic blood pressure.[3] In

[1] Refer to Episodes 37, 79, and 80 for additional information on CVD and oral health.
[2] Tooth loss is an indicator of overall oral health and access to oral healthcare.
[3] Systolic (top number) is the measure of the pressure when the heart ventricles contract and push blood through arteries. Diastolic (bottom number) is the measure of the pressure when the heart relaxes between contractions.

general, tooth loss appeared to be associated with higher risk of hypertension and higher systolic blood pressure. [7]

A systematic review and meta-analysis by Xu et al. (2022) examined the association between tooth loss and hypertension. The authors analyzed 26 studies from 16 different countries involving 1,224,821 participants. Individuals with tooth loss was associated with hypertension. However, the association appeared to be less in the older population, suggesting there may be an initial association between tooth loss and developing hypertension. Results suggest tooth loss and hypertension may have a bidirectional association. The authors recommend oral health clinicians should screen all clients' blood pressure and provide appropriate referrals if hypertension is suspected. Future studies are required to establish causality between tooth loss and hypertension. [9]

Yildirim et al. (2022) found periodontitis severity (stage) and progression rate (grade) may be independent risk factors for hypertension in a cohort of 7,008 clients attending a faculty of dentistry clinic in Turkey. Hypertension was diagnosed in 6% (n=435) of clients. Both periodontal disease stage and grade differed ($p < 0.001$) between clients with or without hypertension. Increased periodontal disease severity was associated with a 20% increasing risk for hypertension in stage IV periodontitis. Increasing periodontitis progression rate was associated with a 35% increased risk for hypertension in grade C periodontitis.[4] [10]

Larvin et al. (2022) conducted a longitudinal cohort study in the UK examining the effect of hypertension and periodontitis on the risk of subsequent systemic disease. The study included 244,393 participants free of systemic disease, other than hypertension at baseline. Self-reported responses of painful gums or loose teeth were surrogates for periodontitis.

Findings demonstrate both periodontitis and hypertension were associated with an increased risk of several subsequent systemic diseases. In particular, hypertension had an additive effect with periodontitis on risks of CVD and respiratory disease. The findings showed participants with loose teeth (clinically indicative of severe periodontitis) had the highest incidence of subsequent systemic diseases compared to the other oral health indicators. The results also suggested periodontitis may independently increase the risk of CVD. Shared inflammatory pathways and endothelial dysfunction[5] are the probable cause in this association. However, further research is required to understand the biological mechanism underpinning the associations between periodontitis, hypertension, and subsequent systemic disease. [11]

A nationwide longitudinal population-based cohort study in Korea by Woo et al. (2021) of 19,680 participants investigated the link between tooth loss and risk of hypertension. Approximately, 1,853 participants (~9% incidence) developed hypertension during the

[4] Refer to Episodes 49 and 50 for discussion on staging and grading periodontal disease.
[5] Endothelial dysfunction is characterized by imbalanced vasodilation and vasoconstriction, elevated reactive oxygen species (ROS), and proinflammatory factors, as well as nitric oxide (NO) deficiency. Endothelial dysfunction disrupts endothelial barrier permeability that is a part of inflammatory response in CVD development. [72]

7.4 years follow-up period. The study demonstrated loss of eight or more teeth was associated with an almost two times higher risk of developing hypertension. Accordingly, higher number of lost teeth may be associated with risk of new-onset hypertension, emphasizing the need to be aware of this risk and monitor for hypertension development in clients with tooth loss. [8]

Kim et al. (2022) investigated whether oral hygiene indicators were linked to major CVD development in 52,677 participants with hypertension in a longitudinal study in Korea. The study found participants with hypertension who had poor oral hygiene indicators (e.g., dental caries) had a higher risk of major cardiovascular events. In contrast, better oral hygiene behaviour (e.g., tooth brushing) was negatively related to the risk of major cardiovascular events. The authors concluded dental caries were related to the risk of CVD in individuals with hypertension. Further, better oral hygiene may attenuate the risk of cardiovascular events in these individuals. [12]

Probable mechanisms

Probable mechanisms for the association between periodontitis and hypertension include:

- Periodontitis may elicit vascular inflammation which leads to endothelial dysfunction.[6]
- Periodontopathogens may stimulate local and systematic host immune responses, resulting in atherosclerosis development and endothelial cell activation.
- Production of reactive oxygen species (ROS)[7] increases in response to periodontal inflammation; subsequently ROS enter the systemic circulation.
- Severe tooth loss may alter dietary habits due to insufficient masticatory function. Reducing intake of vitamins and vegetable fibres increases hypertension risk.
- Systemic inflammation associated with hypertension may activate local inflammation, resulting in release of periodontal inflammatory mediators increasing tooth loss susceptibility.
- Hypertension may lead to malfunction of small arterioles, which affects local nutrition supply, aggravates periodontal diseases, and increases risk of tooth loss. [7] [9]

Atherosclerotic CVD

Atherosclerotic CVD is a leading cause of global disability and death. Atherosclerosis, thickening and hardening of arteries caused by plaque buildup in the inner lining of arteries, can lead to coronary artery disease, peripheral arterial disease, and stroke. Modifying established CVD risk factors can reduce CVD morbidity and mortality.

[6] Endothelium is the single layer of endothelial cells lining all blood and lymphatic vessels. The endothelium has an important role in controlling blood fluidity, platelet aggregation, and vascular tone, and regulating inflammation and angiogenesis (growth of new blood vessels). Endothelial dysfunction is a systemic disorder leading to atherosclerosis and its complications. [73]

[7] Reactive oxygen species (ROS) are oxygen radicals and key signaling molecules that play a vital role in inflammatory disorder progression. Increased ROS generation by polymorphonuclear neutrophils (PMNs) at inflammation sites causes endothelial dysfunction and tissue injury. The vascular endothelium plays a vital role in passage of macromolecules and inflammatory cells from the blood to tissue. Under inflammatory conditions, oxidative stress produced by PMNs leads to the opening of inter-endothelial junctions and promotes migration of inflammatory cells across the endothelial barrier. The migrated inflammatory cells help to clear pathogens and foreign particles, but also lead to tissue injury. [74]

However, other preventive strategies may also contribute to cardiovascular risk improvements. [2] [13] [14]

Periodontal disease is one of the most prevalent chronic infections. According to the Global Burden of Disease Study (2017), periodontal disease was the 11th most prevalent condition in the world, with a prevalence ranging from 20-50%. [15]

Periodontal disease is associated with atherosclerotic CVD, including coronary artery disease, cerebrovascular disease, and peripheral arterial disease. These associations are thought to indirectly operate through systemic inflammatory pathways that can facilitate a series of cascading events causing vascular damage, or through oral pathogen exposure. A systematic review by Sanz et al. (2020) indicated periodontitis may be a modifiable risk factor for CVD.[8] Also, studies have reported specific key pathogens are significantly increased in individuals with periodontal disease and atherosclerosis (e.g., *Streptococcus mutans, Porphyromonas gingivalis*). [16] [17] [18]

Coronary artery disease

Hodel et al. (2023) analyzed genetic information, health data, and blood samples of 3,459 participants in a Swiss population-based cohort study. Approximately 6% of participants experienced at least one coronary artery disease event (e.g., myocardial infarction) during the 12-year follow-up period. Blood samples were tested for antibodies against 22 persistent or frequently recurring pathogens, which included 15 different viruses, six bacteria, and one parasite.

Researchers identified a statistically significant association between the incidence of coronary artery disease and *Fusobacterium nucleatum* infection, after adjusting for all established risk factors. *F. nucleatum* is an anaerobic bacterium that belongs to the normal flora of the oral cavity and plays an important role in the development and progression of oral diseases, such as gingivitis and periodontitis. *F. nucleatum* may contribute to cardiovascular risk through increased systemic inflammation due to oral infection, or through colonization of arterial walls or plaque lining the arterial walls. The study adds to growing evidence inflammation triggered by infections may contribute to coronary artery disease development and increase myocardial infarction risk. [19]

Shi et al. (2016) conducted a meta-analysis of case-controlled studies. Seventeen studies including a total of 3,456 participants who had myocardial infarction (MI group) and 3,875 participants without previous MI (control group) were included.

The MI group had worse periodontal and oral hygiene status and fewer teeth than the control group. The pooled data showed the MI group had higher odds of periodontitis and more serious periodontitis than the control group, and there was a significant association between MI and periodontitis. [20]

[8] Refer to Episode 37 for discussion on 'Periodontitis and cardiovascular diseases: Consensus report' by Sanz et al. (2020).

Nalliah et al. (2023) examined the association between periodontal care with acute myocardial infarction (MI) hospitalization and outcomes in the 30 days after acute care. The analysis included 2,370 individuals with both dental and medical insurance (2016 through 2018) who were hospitalized for acute MI in 2017. Of those, 47% received regular or other oral healthcare, 7% received active periodontal care (root planing and periodontal scaling), and 10% received controlled (maintenance) periodontal care. Prior to acute MI hospitalization, 36% did not receive oral healthcare. Individuals who received periodontal maintenance care had the shortest hospital length of stay. The longest length of stay was experienced by the no-dental-care group. [21] [22]

Coronary artery disease, heart failure, and peripheral artery disease

Joshy et al. (2016) investigated the relationship between oral health and incident hospitalization for various types of CVD, including coronary artery disease, heart failure,[9] ischemic stroke, and peripheral artery disease, and to all-cause mortality. The cohort study included 172,630 individuals aged 45-75 years, without a history of previous CVD at baseline. Data was collected via population health databases and questionnaire, which included self-reported oral health questions, such as number of natural teeth left and self-rated health of teeth and gums. Together, the number of remaining teeth and self-rated oral health, are broad indicators of oral health.

Over two-third (70%) of the cohort had ≥20 teeth and 38% reported 'very good' or 'excellent' health of their teeth and gums. Oral health at baseline differed markedly according to age group, with the 65-75-year-old cohort showing increasing tooth loss and worsening oral health. During a median follow-up of four years, there were 3,239 incident hospitalizations for coronary artery disease, 212 for heart failure, 283 for ischemic stroke, and 359 for peripheral arterial disease, and 1908 deaths.

Results indicated the risk of coronary artery disease, peripheral artery disease and all-cause mortality increased progressively with worsening oral health. The risk of heart failure increased with increasing tooth loss, but not with worsening oral health. No significant differences were observed for ischemic stroke. Compared with those reporting ≥20 teeth left, edentulous[10] individuals had significantly higher relative risks (approximately twofold), for heart failure, peripheral arterial disease, and all-cause mortality. Compared with those reporting 'very good' oral health, those reporting 'poor' oral health had higher risks for coronary artery disease, peripheral arterial disease, and all-cause mortality. The association was generally stronger and more consistent for tooth loss than for self-rated oral health.

The authors concluded tooth loss, and to a lesser extent, self-rated oral health, were associated with increased risk of hospitalization for coronary artery disease, peripheral arterial disease, and all-cause mortality. Tooth loss was also a marker for incident heart failure. Although the relationships were not particularly strong, it is possible markers of

[9] Heart failure, also called congestive heart failure, is a progressive condition characterized by structural and functional cardiac changes, which severely impacts the heart's ability to pump blood. Typical symptoms include dyspnea, ankle swelling, and fatigue.

[10] Tooth loss and edentulism in adults are markers of past periodontal disease and caries.

oral health may have the potential to contribute to cardiovascular screening and prevention, by assisting in the identification of individuals at increased risk. [23]

Yan et al. (2022) investigated the relationship between periodontitis and heart failure using data from the Third National Health and Nutrition Examination Survey (NHANES III) in the US. A total of 13,202 participants (10,606 with no/mild periodontitis; 2,596 with moderate/severe periodontitis) were included in the analysis. Incidence of heart failure in participants with moderate/severe periodontitis was almost six times higher than the no/mild periodontitis group. After adjusting for confounding factors, the results showed incidence of heart failure in the moderate/severe group was three times higher. The authors concluded moderate/severe periodontitis was associated with an increased risk of heart failure. [24]

Atrial fibrosis

Miyauchi et al. (2023) found a significant correlation between periodontitis and atrial fibrosis (scarring to an appendage of the heart's left atrium that can lead to atrial fibrillation) in a sample of 76 individuals with cardiac disease. As part of atrial fibrosis treatment, the left atrial appendage[11] were surgically removed. The researchers analyzed the tissue to determine the correlation between severity of the atrial fibrosis and severity of periodontal disease. They found periodontitis severity was positively and strongly correlated with atrial fibrosis, suggesting periodontal inflammation may intensify cardiac inflammation and disease. The authors concluded periodontitis is likely a risk factor for atrial fibrosis. [25]

Atrial fibrillation

Atrial fibrillation, often called AFib, is the most common type of cardiac arrhythmia. A systematic review by Leelapatana and Limpuangthip (2022) investigated the association between oral health and new-onset atrial fibrillation and atrial fibrillation recurrence.

Five studies met the inclusion criteria, which included three nationwide population-based retrospective cohort studies, one large prospective cohort study, and one case-control study. The studies demonstrated poor oral health was associated with new-onset atrial fibrillation, and may promote atrial fibrillation recurrence and progression. Moreover, individuals with atrial fibrillation and poorer oral health may have a higher risk of arrhythmias and major adverse cardiovascular events during long-term follow-up.

The authors concluded improved oral health potentially reduced new-onset atrial fibrillation. Further, periodontitis prevention, regular oral healthcare visits for professional dental scaling, and frequent tooth brushing, are oral healthcare interventions that may contribute to atrial fibrillation protection. Thus, promoting oral health should be integrated as a part of primary atrial fibrillation prevention. [26]

Cerebrovascular disease

Preliminary research presented at the February 2023 American Stroke Association's International Stroke Conference showed individuals with a genetic predisposition to oral

[11] The left atrial appendage is a pouch-like structure in the left atrium.

health problems (e.g., dental caries, missing teeth) were more likely to demonstrate damage to the microstructure of the brain and increased risk for silent cerebrovascular disease. Between 2014 and 2021, approximately 40,000 adults (46% male, average age 57 years) without a history of stroke were screened for 105 genetic variants known to predispose individuals to have cavities, dentures, and missing teeth later in life. Signs of poor brain health were screened via MRI images of the participants' brains. The relationship between genetic risk factors for poor oral health and brain health was evaluated. The study found adults genetically prone to poor oral health may be more likely to show signs of declining brain health than those with healthy teeth and periodontal tissues. The study suggests early intervention to improve oral hygiene, and in turn oral health, may improve brain health. [27]

Oral microbiome

The oral cavity has the second largest and diverse microbiota, after the gut, harbouring over 700 oral microbes, including bacteria, fungi, viruses, and protozoa. In addition to being the initiation point of digestion, the oral microbiome is crucial in maintaining oral and systemic health. [28]

Oral dysbiosis is an imbalance in oral flora. Depending on the type of bacterial imbalance, dysbiosis can lead to various oral pathologies. Several modifiable factors, including salivary gland impairment, poor oral hygiene, gingival inflammation, dietary habits, and smoking may lead to oral dysbiosis, which can cause localized chronic oral inflammation.

Oral dysbiosis is thought to be linked to CVD. Various species including, *Streptococcus mutans* and *P. gingivalis*, have been shown to increase with the occurrence of periodontal disease and systemic inflammation. Several other species, mainly *Treponema denticola, Tannerella forsythia, Prevotella intermedia, Prevotella nigrescens, Actictinobacillus actinomycetemcomitan, Campylobacter rectus, P. gingivalis*, *Porphyromonas endodontalis, Prevotella intermedia, Eubacterium brachy*, and *Eubacterium saphenum*, have also been found to be associated with oral dysbiosis and CVD. [18]

Oral microbiota related to CVD [18] [29]

Disorder*	Bacterial species*
Systemic inflammation	*Eubacterium brachy* *Eubacterium saphenum* *Porphyromonas endodontalis*
Atherosclerosis	*Actictinobacillus actinomycetemcomitan* *Campylobacter rectus* *Porphyromonas gingivalis* *Porphyromonas endodontalis* *Prevotella intermedia* *Prevotella nigrescens*
Peripheral artery disease	*Aggregatibacter actinomycetemcomitan* *Prevotella intermedia* *Porphyromonas gingivalis*

Disorder*	Bacterial species*
	Streptococcus mutans *Tannerella forsythia* *Treponema denticola*
Hypertension	*Porphyromonas gingivalis*
Abdominal aortic aneurysm	*Aggregatibacter actinomycetemcomitan*

*Nonexhaustive list

Oral dysbiosis is the major causative factor of oral diseases (e.g., dental caries, periodontal disease). It represents a pathogenic risk factor for CVD development, including atherosclerosis, coronary artery disease, and valvular heart disease. For example, research has revealed a breakdown of the symbiotic relationship of resident microbiome increases the risk of various harmful microbes translocating from the oral cavity to heart valves, which may lead to permanent valve damage.

Neculae et al. (2023) reviewed the pathophysiological link between oral dysbiosis and valvular heart disease, focusing on the microorganisms involved, prevention, and potential therapeutic applications in valvular heart disease management.

The authors discussed the link between oral dysbiosis and valvular heart disease, including the role of saliva, dental plaque, oral mucosa colonization, and periodontitis, as well as the detection of oral bacteria in cardiovascular tissues. For example:

- Saliva plays a significant role in oral microbiome structure through immune components with antibacterial properties (e.g., lysozyme, lactoferrin, immunoglobulins, histidine-rich proteins, the peroxidase system). Salivary glycoproteins provide the bacteria's nutrition, and proteins (e.g., mucin) can prevent microorganism adherence to oral surfaces. All these elements contribute to maintaining biofilm and oral microbiome balance. Small changes or insufficient salivary flow can lead to oral dysbiosis.
- Dysbiosis in supragingival dental plaque composition is one of the first steps in developing disease conditions (e.g., dental caries, periodontal disease).
- Oral mucosa colonization is known to influence the development of dental caries and periodontal disease.
- Severity and progression rate of periodontitis is an independent risk factor for valvular heart disease. Sia et al. (2021) showed intensive treatment of periodontitis significantly lowered risk for valvular heart disease development. [30]
- Oral bacterial DNA has been detected in cardiovascular tissue specimens from the aortic and mitral valve, aortic aneurysmal wall, and atrial and ventricular myocardium, linking oral bacteria to CVD development.

The authors concluded more research is required to fully understand the mechanisms by which oral microorganisms contribute to valvular heart disease development. However, by focusing on periodontal disease prevention that targets the oral microbiome can benefit quality of life. Simple steps, such as host modulation, oral hygiene, and diet, can contribute to oral eubiosis. Furthermore, using available therapies, including prebiotics and probiotics may offer new directions. Antimicrobial peptides, nanoscale drug delivery systems, vaccines, and even oral microbiota

transplant are potential new options requiring further study to generate additional therapeutic approaches. [31]

Oral microbiota are thought to influence blood pressure regulation. Certain oral bacteria, through nitrate-nitrite metabolism, provide the host with a source of bioactive nitric oxide, a vasodilator critical to arterial blood pressure regulation. These bacteria are referred to as nitrate-reducing bacteria. However, it is plausible other oral bacteria, through nonnitrate pathways, might impact blood pressure regulation through arterial atherosclerosis and endothelial dysfunction.

LaMonte et al. (2022) examined associations between oral microbiota, blood pressure, and incident hypertension in 1,215 postmenopausal participants, with a mean follow-up of 10 years. In the prospective analysis, ten oral bacterial species were significantly associated with higher risk of developing incident hypertension (e.g., *Streptococcus anginosus, Streptococcus salivarius,* certain *Prevotella sp.*) and five were significantly associated with lower risk of incident hypertension (e.g., *Neisseria subflava, Aggregatibacter segnis*). Only one of the five bacteria (*N. subflava*) is a known nitrate reducer.

The authors concluded specific oral bacteria were associated with risk of hypertension development among postmenopausal females. Nonnitrate reduction mechanisms, such as inflammation and atherosclerosis, may be involved. Research to confirm these observations and elucidate mechanisms is needed. [32]

Probable mechanisms

Oral infections can lead to chronic inflammation affecting teeth (caries), gingival tissues (gingivitis, endodontic lesions), and the periodontium (periodontitis). At least four basic pathogenic mechanisms have been proposed to explain the relationship between oral inflammation and atherosclerosis:

- Low level bacteremia where oral bacteria (or their by-products) enter the blood stream and invade arterial walls and atherosclerotic plaques.
- Increased systemic inflammation induced by inflammatory mediators released from oral inflammation sites into the blood stream.
- Autoimmunity to host proteins caused by the host immune response to specific components of oral pathogens.
- Proatherogenic effects resulting from specific bacterial toxins released by oral pathogenic bacteria. [33] [34]

Other factors linking periodontitis and CVD include:

- Higher incidence of bacteremia in individuals with periodontal disease, potentially causing various effects systemically.
- More virulent bacteria are present in periodontitis, resulting in greater inflammation, which may trigger events with an adverse effect on general health.
- Periodontitis pathogens (e.g., *P. gingivalis*) promote atheroma formation and accelerate atherosclerosis.

- Periodontal pathogens generate antibodies (anticardiolipin antibodies) that might eventually cross-react with the cardiovascular system, possibly contributing to CVD onset.
- Individuals with periodontitis have higher levels of:
    - C-reactive protein (CRP).
    - Cytokines and inflammatory mediators, which have been associated with a higher incidence of CVD.
    - Fibrinogen (thrombotic factors).
    - Traditional CVD risk factors (e.g., cholesterol, low-density lipoproteins (LDL), triglycerides, very-low-density lipoproteins (VLDL), oxidized LDL, etc.).
- Periodontitis and CVD share the same genetic factors. There is a specific area on chromosome 9 associated with coronary artery disease, ischemic stroke, type 2 diabetes, and Alzheimer's disease and is also consistently associated with periodontitis. [17] [35]

Periodontal therapy

It is unclear if treating periodontal disease can prevent the onset of CVD or secondary events.

Yamada et al. (2022) explored the association between regular oral healthcare visits and atherosclerosis among 602 community dwellers aged ≥55 years in Japan. The authors found regular oral healthcare visits were associated with a reduced presence of atherosclerosis. A biological mechanism for this association is oral healthcare awareness and improvements in oral health behaviours from regular oral healthcare visits may attenuate the risk of periodontitis and tooth loss, which can contribute to controlling atherosclerosis progression. Previous studies have reported regular oral healthcare visits are associated with higher oral health literacy and lower risk of periodontitis and tooth loss. [36]

Liu et al. (2022) conducted a meta-analysis of six randomized controlled trials (RCTs) to assess the influence of nonsurgical periodontal therapy (NSPT) on individuals with coronary artery disease and periodontitis. The studies enrolled 619 participants (360 in intervention group; 259 in control group). All participants in the intervention group received supra- and subgingival scaling and root planing, including oral self-care instructions. The control group received no periodontal therapy or delayed therapy.

Outcomes that were measured included CRP and interleukin-6 (IL-6),[12] flow-mediated dilation,[13] and lipid metabolism parameters (e.g., triglyceride, total cholesterol, LDL, and high-density lipoprotein [HDL]).

Researchers found a significant reduction of CRP with NSPT in participants with coronary artery disease and periodontitis, with limited evidence NSPT positively affected IL-6, flow-mediated dilation, and lipid metabolism parameters. The authors concluded NSPT can be considered an important preventive strategy for major

[12] CRP and IL-6 are indicators of systemic inflammation.
[13] Flow-mediated dilation is an indicator of endothelial function.

cardiovascular events in coronary artery disease. However, there is a need for more RCTs to investigate the efficacy of NSPT in individuals with coronary artery disease and periodontitis, including longer-term follow-up. [37]

Roca-Millan et al. (2018) conducted a systematic review and meta-analysis to analyze the effect of periodontal treatment on cardiovascular risk parameters in individuals with atherosclerotic CVD. Ten clinical trials with a total population of 669 (390 in intervention groups; 279 in control groups) were analyzed. Periodontal treatment performed in the studies reviewed consisted of mechanical debridement (n=390) in all intervention cases, complemented by oral hygiene instruction in most cases.

Periodontal treatment reduced CRP (78%), tumour necrosis factor-alpha [TNF-α] (67%), IL-6 (100%), and leukocytes (50%). Fibrinogen levels improved considerably (67%). Effects on lipid parameters were more limited, whereby only oxidized LDL and VLDL cholesterol decreased significantly. Meta-analysis showed a statistically significant decrease in CRP and leukocytes values with nonsurgical periodontal treatment in contrast to no treatment.

The authors concluded periodontal treatment can improve some biochemical parameters involved in CVD development, including CRP, TNF-α, IL-6, fibrinogen, leukocytes, oxidized LDL, and VLDL. Further RCTs are necessary, with longer follow-up periods, including regular periodic monitoring, to determine the impact of periodontal treatment. [38]

A systematic review by Goyal et al. (2023) investigated whether periodontal therapy was an effective treatment modality for preventing or managing CVD in individuals with periodontitis. The authors concluded there was very limited evidence assessing the impact of periodontal therapy on CVD prevention, and evidence was insufficient to generate any implications for practice. Further RCTs are needed before reliable conclusions can be drawn. [39]

A Cochrane review by Ye et al. (2022) investigated the effects of periodontal therapy for primary or secondary prevention of CVD in individuals with chronic periodontitis.[14] For primary prevention of CVD in individuals with periodontitis and metabolic syndrome, the very low-certainty evidence was inconclusive about the effects of scaling and root planing plus antibiotics compared to supragingival scaling. There was no reliable evidence available regarding secondary prevention of CVD in individuals with chronic periodontitis and CVD. Further trials are needed to determine whether periodontal treatment can help prevent occurrence or recurrence of CVD. [40]

A Cochrane review by Luo et al. (2021) assessed the effect of different periodontal treatment on blood pressure in individuals with chronic periodontitis. The authors stated conclusions could not be drawn about the effect of periodontal treatment on blood pressure in individuals with chronic periodontitis due to low certainty of evidence and

[14] The authors acknowledged the AAP periodontal classification system but used the term 'chronic periodontitis' because reviewed studies were based on this terminology.

lack of relevant studies. Only one study was found suggesting periodontal treatment may reduce systolic blood pressure and diastolic blood pressure over a short period in individuals with hypertension and chronic periodontitis, but the certainty of evidence was moderate. [41]

However, a systematic review and meta-analysis of randomized clinical trials by Luthra et al. (2022) showed when individuals received nonsurgical periodontal treatment versus no treatment, there was a significant decrease in their CRP, up to six months follow-up. The reduction was to a degree equivalent to that observed after traditional lifestyle or drug interventions. Secondary outcomes included changes in levels of other inflammatory biomarkers (IL-6, IL-8, IL-10, and TNF-α); along with changes in periodontal measures of inflammation (bleeding on probing, gingival pocket probing, clinical attachment levels). The authors concluded the evidence supported a causal association between periodontitis and systemic inflammation. [42]

Randomized controlled trials

Challenges involved in conducting a RCT include:

- Periodontitis is slowly progressive and effect on CVD is small, therefore a large number of participants would need to be reviewed over a long period to observe significant differences in CVD endpoints.
- Establishing an appropriate control group in whom periodontal treatment is withheld over a long observation period is not ethically feasible.
- Cost of doing these studies is expensive. [4]

Impact of CVD on oral health

Research has shown some CVD medications can increase risk for oral disease. Common antihypertensive drugs can reduce normal salivation, including diuretics, beta blockers, and calcium channel blockers. Dry mouth can cause altered taste, mouth ulcers, cracked lips, difficulty chewing, dysphagia, halitosis, and burning mouth. Hyposalivation can exacerbate periodontal disease and tooth decay, increasing risk for tooth loss, which contributes to masticatory dysfunction. In turn, this can negatively impact nutritional intake, with the potential to further compromise management of underlying CVD.

Calcium channel blockers can contribute to gingival hyperplasia. ACE inhibitors and beta blockers can alter taste. Anticoagulants (e.g., warfarin) may result in increased and/or prolonged oral bleeding. Petechiae may occur in the oral cavity with endocarditis. Pain may radiate to mandible and teeth during a severe angina attack or MI. [4] [43] [44] [45] [46] [47]

Oral effects of cardiovascular drugs [45] [47] [48] [49] [50] [51] [52] [53]

Oral adverse effect*	Drug*
Angioedema of lips, face, tongue	ACE inhibitors (captopril, enalapril, lisinopril)
	Angiotensin II receptor blockers (ARBs) (candesartan, olmesartan, telmisartan, valsartan)
	Direct renin inhibitors (DRI) (aliskiren)
	Beta blockers (metoprolol, propranolol)
	Calcium channel blockers (amlodipine, nicardipine)
	Diuretic (furosemide)
	Potassium channel blockers (amiodarone)
Aphthae/ulcerations	ARBs (candesartan, irbesartan, losartan)
	Potassium channel activators (nicorandil)
	Beta blockers (labetalol)
Bleeding (e.g., petechiae, hematomas, gingival bleeding, increased and/or prolonged oral bleeding)	Antiplatelets (clopidogrel, ticlopidine, prasugrel, ticagrelor, aspirin)
	Anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban)
Burning mouth syndrome	ACE inhibitors (captopril, lisinopril)
Cheilitis	Statins (simvastatin)
Chronic cough	ACE inhibitors
Dry mouth	Alpha-2 agonists (clonidine, guanfacine, methyldopa)
	Alpha-1 blockers (terazosin)
	ACE inhibitors (captopril, enalapril, lisinopril)
	Diuretics (furosemide)
	Calcium channel blockers (diltiazem, nifedipine, verapamil)
	Vasodilators (sublingual nitroglycerin)
Dysgeusia (taste changes)	ACE inhibitors (captopril)
	ARBs (e.g., candesartan, eprosartan, losartan, valsartan)
	Beta blockers (metoprolol, propranolol)
	Calcium channel blockers (amlodipine, nifedipine)
	Other (clopidogrel, midodrine)
Gingival hyperplasia (enlargement)	Calcium channel blockers (amlodipine, diltiazem, nifedipine, verapamil)
	Sodium channel blockers (phenytoin)
Glossitis	Potassium channel activators (nicorandil)
Hypersalivation	Cardiac glycosides (digoxin, digitoxin)
Increased gag reflex	Cardiac glycosides (digoxin, digitoxin, digitalis)
Lichenoid lesions (lichen planus-like symptoms)	Beta blockers (labetalol, metoprolol, propranolol))
	ACE inhibitors
	Alpha-2 agonists (methyldopa)
Pemphigus-like symptoms	ACE inhibitors (captopril, lisinopril)

*Nonexhaustive list.

Oral manifestations of CVD [46] [47] [50] [54] [55] [56]

Type of CVD*	Oral manifestation*
Angina	Pain radiating into the mandible and teeth.
Myocardial infarction	Pain radiating into the mandible and teeth. Possibly cyanosis of the lips and/or mucous membranes.
Endocarditis	Petechiae on oral mucosa.
Heart failure	Mucous membranes may be grayish-blue with severe heart failure. Cyanosis (bluish hue) of the lips and ashen-gray appearance of perioral skin.
Stroke	Unilateral face drooping or sudden numbness. Post stroke: dysphagia, oral discomfort and pain, oral infections (especially oral candidiasis), and difficulties in denture wearing. Impaired gag reflex, slurred speech, and difficulty chewing. Taste changes. Periodontal disease and dental caries due to poor oral hygiene.

*Nonexhaustive list.

CVD risk factors

Factors with detrimental impact on cardiovascular health and increase the risk of hypertension include sedentary habits, high blood glucose, hyperlipidemia, excessive body weight, low vegetables consumption, smoking, alcohol use, recreational drug use, high-salt diet, poor sleep, and mental health disorders.[15]

For example, a review by Barris et al. (2022) found females of all ages and ethnicities are more salt sensitive than males. The tendency to hold onto more salt increases after menopause, which may have implications for blood pressure control. Some individuals can effectively excrete higher salt intake, so it does not increase their blood pressure. However, for many, changes in dietary salt intake can cause noticeable increases or decreases in blood pressure. These individuals are considered salt sensitive. The study suggests salt sensitivity is a factor in about half of the cases where cause of hypertension is not apparent and often contributes to treatment-resistant hypertension.

Heart and Stroke Foundation of Canada recommends Canadians consume no more than 2,300 mg of sodium (1 teaspoon/5 mL table salt) a day. This includes the amount of salt individuals add to their food, as well as salt already added in large quantities to prepared foods, canned products, snack foods, and restaurant meals. [57] [58] [59]

The 'World Health Organization (WHO) Report on Sodium Intake Reduction' shows the world is off-track to achieve its global target of reducing sodium intake by 30% by 2025. The report shows only 5% of WHO Member States are protected by mandatory and comprehensive sodium reduction policies, and 73% of WHO Member States lack implementing full range of such policies.

The global average salt intake is estimated to be ~11 grams per day, more than double the WHO recommendation of less <5 grams of salt per day. Sodium increases the risk of CVD and premature death when eaten in excess. More evidence is emerging linking

[15] Refer to Episode 79 for more information on CVD risk factors.

high sodium intake and increased risk of other health conditions, such as gastric cancer, obesity, osteoporosis, and kidney disease.

Implementing highly cost-effective sodium reduction policies could save an estimated seven million lives globally by 2030. But currently, only nine countries (Brazil, Chile, Czech Republic, Lithuania, Malaysia, Mexico, Saudi Arabia, Spain, Uruguay) have a comprehensive package of recommended policies to reduce sodium intake. Canada has instituted voluntary measures to reduce sodium in the food supply and by encouraging consumers to make healthier food choices about sodium.

A comprehensive approach to sodium reduction includes adopting mandatory policies and interventions related to sodium, including:

- Reformulating foods to contain less salt, and setting sodium target amounts in foods and meals.
- Establishing public food procurement policies to limit sodium rich foods in public institutions (e.g., hospitals, schools, workplaces, nursing homes).
- Front-of-package labelling that helps consumers select lower sodium products.
- Behaviour change communication and mass media campaigns to reduce sodium consumption.

Mandatory sodium reduction policies are more effective, as they achieve broader coverage and safeguard against commercial interests, while providing a level playing field for food manufacturers. WHO calls on nations to do more to reduce sodium consumption. WHO also calls on food manufacturers to set ambitious sodium reduction targets in their products. [60] [61] [62] [63]

Poor sleep is associated with a shorter lifetime for cardiovascular health, according to a study by Huang, et al (2023) of over 300,000 participants. The study suggests individuals with sleep apnea are most at risk of poorer cardiovascular health. [64]

Research by Yuan et al. (2023) found a significant link between inadequate sleep and an increased likelihood of developing peripheral artery disease. Peripheral arterial disease results from obstructed arteries in legs and increases risk of coronary artery disease, stroke, and myocardial infarction. Researchers examined data from 650,000 participants and found those who slept less than 5 hours per night had a 74% higher chance of developing peripheral arterial disease, compared to those who consistently slept 7 to 8 hours a night. They also noted having peripheral arterial disease may be a factor in inadequate sleep. The study emphasizes the importance of proper sleep to maintain vascular health and prevent peripheral arterial disease onset. [65]

Depression may increase stroke risk. An international study by Murphy et al. (2023) found individuals with depressive symptoms had an increased risk of both ischemic and hemorrhagic stroke, and worse recovery after a stroke. The study showed individuals with symptoms of depression had a 46% increased stroke risk compared with those without such symptoms. The authors suggest appropriate treatment for depression, including psychological interventions, might lessen the risk of stroke. [66]

Prevention through oral health

Regular oral health screening may reduce the risk of CVD. In a retrospective cohort study by Kim et al. (2021), investigators followed 478,245 adults for 11 years and observed a lower risk of major adverse cardiovascular events among participants who underwent oral health screenings compared to those who did not. The association may be attributed to healthy habits of participants in the screening group. However, it is possible the improvement of oral health through oral health screening influenced CVD prevention. [67]

A study by Janket et al. (2023) revealed good oral self-care encompassing both brushing and flossing was associated with significantly lower risk of cardiovascular mortality compared with poor oral self-care during a median follow-up of ~19 years. Adding mouthwash did not help beyond the benefits of good brushing and flossing. Individuals with coronary artery disease experienced a marginally significant decrease in cardiovascular mortality risk with good oral self-care. Brushing and flossing are relatively inexpensive and have low risk of adverse effects. Moreover, even those who already have CVD may lower CVD mortality risk by maintaining good oral hygiene. [68]

Del Pinto et al. (2022) investigated the association of self-care habits and hypertension. Among the 4,506 participants, 48% reported brushing ≥3 times/day, and 23% used a power toothbrush. Brushing ≥3 versus <3 times/day and use of power versus manual toothbrush were associated with 19% and 28% lower odds of hypertension, respectively.

Possible mechanisms behind the systemic benefit of oral self-care include their modulating effects on the local microbiota and the immune system. Previous research has shown:

- Periodontal bacteria appear to elicit a hypertension-specific immune host response;
- Periodontal treatment has a significant modulatory effect on adaptive immunity;[16] and
- Periopathogenic bacteria were positively associated with both blood pressure and prevalent hypertension.

Thus, regular oral self-care might represent an additional, nonpharmacological strategy for CVD prevention, possibly through dysbiosis reversal and systemic anti-inflammatory effects. Future research is required to test whether oral self-care may represent a complementary approach to manage hypertension. [69]

Park et al. (2018) performed a population-based study in Korea using nationwide data of 247,696 healthy adults aged ≥40 years with no history of major cardiovascular events to assess the impact of self-reported oral self-care on the occurrence of CVD. After a median follow-up of 9.5 years, 14,893 major cardiovascular events occurred, including cardiac death, myocardial infarction, stroke, and heart failure. The risk of cardiovascular events was higher in participants with periodontal disease, a higher number of dental caries, or more tooth loss. Performing one or more tooth brushing a day was associated

[16] Refer to Episodes 44 and 45 for discussion on the immune system.

with a 9% significantly lower risk of cardiovascular events. Tooth brushing three times a day or more was associated with a 19% reduction in cardiovascular events compared with tooth brushing once or less a day. Regular oral healthcare visits (once a year or more) for professional cleaning were also shown to reduce cardiovascular risk by 14%. Improved oral hygiene behaviours were shown to attenuate the cardiovascular risk originating from periodontal disease, dental caries, and tooth loss.

Several mechanisms were proposed to explain this benefit, including:

- Periodontal disease causes chronic inflammation. A reduction in inflammatory markers such as CRP and interleukins have been reported in association with regular tooth brushing as well as periodontal treatment.
- Oral hygiene has been suggested to modify major risk factors such as diabetes and dyslipidemia.
- Oral hygiene alters oral microbiota. Increasing evidence suggests microbiota play a role in the pathogenesis of atherosclerotic CVD and heart failure. Various bacteria have been detected in human atherosclerotic plaques, which are linked with oral microbiota.

The study's findings suggest the importance of early intervention and simple behavioural change in oral self-care may help prevent future cardiovascular events. [70]

New advances

A study aiming to develop and test a machine learning model to predict CVD using oral infection indicators was presented at the 52nd annual meeting of the American Association for Dental, Oral and Craniofacial Research (AADOCR) in March 2023. The study analyzed the relationship between self-reported CVD (e.g., heart surgery, heart valve, arrythmia, congenital heart disease) and markers for oral infections in 5,188 participants. Periodontal screening and recording (PSR) data and decayed, missing, or filled teeth and surfaces (DMFT and DMFS) were used in the analyses.

Results showed a significant association between both DMFT and DMFS and CVD, independent of sex and tobacco use. The results of the analysis between DMFS and CVD also remained significant after controlling for participants' age. The machine learning model demonstrated 84% accuracy in predicting CVD based on an individual's DMFS score.

The study confirmed an association between dental caries and CVD and highlighted the potential for machine learning methods to improve CVD prediction using indicators of oral infections. Future directions include assessing if artificial intelligence can help predict improvement in CVD markers with dental caries management. [71]

Take home messages

- Educate clients about the connection between oral health and cardiovascular health, including the importance of regular oral health appointments and good oral self-care.
- Screen all clients for hypertension and refer to medical practitioners for further assessment as warranted.

- Assess for common CVD and periodontal disease risk factors, such as tobacco use, stress, obesity, sedentary lifestyle, diabetes, and poor diet. Advise clients to actively manage their risk factors to reduce their lifetime risk of related diseases. This would include smoking cessation, and healthy eating by following Canada's Food Guide.
- Research indicates individuals with periodontitis have an increased risk for CVD events. More severe stages of periodontitis are associated with a higher CVD risk. Periodontal therapy has been shown to reduce systemic inflammatory burden. Thus, individuals diagnosed with CVD, or related risk factors (e.g., hypertension, hyperlipidemia) should be encouraged to maintain good oral health, and seek professional assessment and management of their periodontal health, since reducing the oral inflammatory burden may lower their CVD risk. [4] [17]

References

[1] American Dental Association, "Oral-Systemic Health," 23 December 2021. [Online]. Available: https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/oral-systemic-health. [Accessed 18 March 2023].

[2] Gianos, E; Jackson, E; Tejpal, A, et al., "Oral health and atherosclerotic cardiovascular disease: A review," *American Journal of Preventive Cardiology,* vol. 17, article 100179, pp. 1-7, September 2021.

[3] American Dental Association, "Periodontitis," 9 June 2022. [Online]. Available: https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/periodontitis. [Accessed 18 March 2023].

[4] S. King, C. Chow and J. Eberhard, "Oral health and cardiometabolic disease: Understanding the relationship," *Internal Medicine Journal,* vol. 52, no. 2, pp. 198-205, 20 February 2022.

[5] K. Mills, Stefanescu, A and H. J, "The global epidemiology of hypertension," *Nature Reviews Nephrology,* vol. 16, no. 4, pp. 223-237, 2020.

[6] G. Roth, G. Mensah, C. Johnson, et al., "Global burden of cardiovascular diseases and risk factors, 1990–2019: Update from the GBD 2019 Study," *Journal of the American College of Cardiology,* vol. 76, no. 25, pp. 2982-3021, December 2022.

[7] A. Tada, R. Tano and H. Miura, "The relationship between tooth loss and hypertension: a systematic review and meta-analysis," *Scientific Reports,* vol. 12, article 13311, pp. 1-13, 3 August 2022.

[8] H. Woo, Y. Chang, J. Lee and T. Song, "Tooth loss is associated with an increased risk of hypertension: A nationwide population-based cohort study," *PL0S ONE,* vol. 16, no. 6, pp. 1-11, 15 June 2021.

[9] K. Xu, W. Yu, Y. Li, et al., "Association between tooth loss and hypertension: A systematic review and meta-analysis," *Journal of Dentistry,* vol. 123, article 104178, August 2022.

[10] B. Yildirim, C. Aksit, M. Mutlu, et al., "Severity and progression rate of periodontitis are associated with an increased risk of hypertension of patients attending a university clinic," *BMC Oral Health,* vol. 22, article 627, pp. 1-9, 22 December 2022.

[11] H. Larvin, J. Kang, V. Aggarwal, et al., "The additive effect of periodontitis with hypertension on risk of systemic disease and mortality," *Journal of Periodontology,* vol. 93, no. 7, pp. 1024-1035, 23 April 2022.

[12] J. Kim, H. Kim, J. Jeon and T. Song, "Association between oral health and cardiovascular outcomes in patients with hypertension: A nationwide cohort study," *Journal of Hypertension,* vol. 40, no. 2, pp. 374-381, February 2022.

[13] John Hopkins Medicine, "Atherosclerosis," 2023. [Online]. Available: https://www.hopkinsmedicine.org/health/conditions-and-diseases/atherosclerosis. [Accessed 24 March 2023].

[14] National Research Council (US) Committee on Diet and Health, "Atherosclerotic Cardiovascular Diseases," in *Diet and Health: Implications for Reducing Chronic Disease Risk.*, Washington, DC, Academies Press, 1989.

[15] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, "Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017," *Lancet,* vol. 392, no. 10159, pp. 1789-1858, 10 November 2018.

[16] US Department of Health and Human Services, "Oral Health in America: Advances and Challenges," 2021. [Online]. Available: https://www.nidcr.nih.gov/research/oralhealthinamerica. [Accessed 19 March 2023].

[17] M. Sanz, A. del Castillo, S. Jepsen, J. Gonzalez-Juanatey, F. D'Aiuto, P. Bouchard, I. Chapple, T. Dietrich, I. Gotsman, G. Graziani, D. Herrera, B. Loos, P. Madianos, J. Michel, P. Perel, B. Pieske, L. Shapira, M. Shechter, M. Tonetti, C. Vlachopoulos and W, "Periodontitis and cardiovascular diseases: Consensus report," *Journal of Clinical Periodontology,* vol. 47, no. 3, pp. 268-288, 3 February 2020.

[18] Y. Li, M. Zhu, Y. Liu, et al., "The oral microbiota and cardiometabolic health: A comprehensive review and emerging insights," *Frontiers in Immunology,* vol. 13, pp. 1-15, 18 November 2022.

[19] F. Hodel, Z. Xu, C. Wandall, et al., "Associations of genetic and infectious risk factors with coronary heart disease," *eLife,* vol. 16, pp. 1-22, 14 February 2023.

[20] Q. Shi, B. Zhang, N. Huoetal., "Association between myocardial infarction and periodontitis: A meta-analysis of case-control studies," *Frontiers in Physiology,* vol. 7, article 519, pp. 1-12, 4 November 2016.

[21] R. Nalliah, T. Basu and C. Chang, "Association between periodontal care and hospitalization with acute myocardial infarction," *JADA,* vol. 153, no. 8, pp. 776-786, 19 April 2022.

[22] University of Michigan, "People who receive periodontal care have better outcomes after heart attack," 15 September 2022. [Online]. Available: https://news.umich.edu/people-who-receive-periodontal-care-have-better-outcomes-after-heart-attack/. [Accessed 22 March 2023].

[23] G. Joshy, M. Arora, R. Korda, J. Chalmers and E. Banks, "Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause

mortality? Findings from 172 630 participants from the prospective 45 and Up Study," *BMJ Open,* vol. 6, pp. 1-10, 2016.

[24] Y. Yan, M. Mao, Y. Li, et al., "Periodontitis is associated with heart failure: A population-based study (NHANES III)," *Frontiers in Physiology,* vol. 13, article 854606, pp. 1-8, 20 April 2022.

[25] S. Miyauchi, H. Nishi, K. Ouhara, et al., "Relationship between periodontitis and atrial fibrosis in atrial fibrillation: Histological evaluation of left atrial appendages," *JACC: Clinical Electrophysiology,* vol. 9, no. 1, pp. 43-53, January 2023.

[26] P. Leelapatana and N. Limpuangthip, "Association between oral health and atrial fibrillation: A systematic review," *Heliyon,* vol. 8, no. 3, pp. 1-9, 23 March 2022.

[27] American Heart Association, Inc., "Poor oral health may contribute to declines in brain health," 2 February 2023. [Online]. Available: https://newsroom.heart.org/news/poor-oral-health-may-contribute-to-declines-in-brain-health. [Accessed 22 March 2023].

[28] P. Deo and R. Deshmukh, "Oral microbiome: Unveiling the fundamentals," *Journal of Oral and Maxillofacial Pathology,* vol. 23, no. 1, pp. 122-128, January-April 2019.

[29] E. Kozarov, B. Dorn, C. Shelburne, W. Dunn and A. Progulske-Fox, "Human atherosclerotic plaque contains viable invasive Actinobacillus actinomycetemcomitans and Porphyromonas gingivalis," *Arteriosclerosis, Thrombosis and Vascular Biology,* vol. 25, pp. e17-e18, 20 January 2005.

[30] S. Sia, M. Jan, y. Wang, Y. Huang and J. Wei, "Periodontitis is associated with incidental valvular heart disease: A nationwide population-based cohort study," *Journal of Clinical Periodontology,* vol. 48, no. 8, pp. 1085-1092, 1 June 2021.

[31] E. Neculae, E. Gosav, E. Valasciuc, et al., "The oral microbiota in valvular heart disease: Current knowledge and future directions," *Life,* vol. 13, no. 1, pp. 1-20, 8 January 2023.

[32] M. LaMonte, J. Gordon, P. Diaz-Moreno, et al., "Oral Microbiome Is Associated With Incident Hypertension Among Postmenopausal Women," *Journal of the American Heart Association,* vol. 11, no. 6, 2 March 2022.

[33] G. Aarabi, G. Heydecke and U. Seedorf, "Roles of oral infections in the pathomechanism of atherosclerosis," *International Journal of,* vol. 19, no. 7, pp. 1-12, 6 July 2018.

[34] Z. Corredor, A. Suarex-Molina, C. Fong, et al., "Presence of periodontal pathogenic bacteria in blood of patients with coronary artery disease," *Scientific Reports,* vol. 12, article 1241, pp. 1-11, 24 January 2022.

[35] European Federation of Periodontoogy, "Perio & Cardio Recommendations for the oral-healthcare team," [Online]. Available: https://www.efp.org/fileadmin/uploads/efp/Documents/Campaigns/Perio_and_Cardio/Recommendations/Perio_cardio-Recomm-01-OralHcTeam.pdf. [Accessed 24 March 2023].

[36] S. Yamada, T. Komiyama, T. Ohi, et al., "Regular dental visits, periodontitis, tooth loss, and atherosclerosis: The Ohasama study," *Journal of Periodontal Research,* vol. 57, no. 3, pp. 615-622, 6 April 2022.

[37] C. Liu, F. Shi, W. Li and J. Chen, "Efficacy of non-surgical periodontal treatment on patients with coronary artery disease: A meta-analysis of randomized controlled trials," *Med Oral Patol Oral Cir Bucal,* vol. 27, no. 6, pp. e578-e587, November 2022.

[38] E. Roca-Millan, B. González-Navarro, M. del Mar Sabater-Recolons, et al., "Periodontal treatment on patients with cardiovascular disease: Systematic review and meta-analysis," *Med Oral Patol Oral Cir Bucal,* vol. 23, no. 6, pp. e681-e690, November 2018.

[39] L. Goyal, S. Gupta, M. Dewan and M. Singla, "Is periodontal therapy an effective treatment modality for preventing or managing cardiovascular disease in patients with periodontitis?," *Evidence-Based Dentistry,* vol. 24, pp. 32-34, 08 March 2023.

[40] Z. Ye, Y. Cao, C. Miao, et al., "Periodontal therapy for primary or secondary prevention of cardiovascular disease in people with periodontitis," *Cochrane Database of Systematic Reviews,* no. 10, 22 October 2022.

[41] Y. Luo, H. Ye, W. Liu, Z. Lv, Y. Jia, C. Li and Y. Zhang, "Effect of periodontal treatments on blood pressure," *Cochrane Database of Systematic Reviews,* no. 12, 12 December 2021.

[42] S. Luthra, M. Orlandi, S. Hussain, et al., "Treatment of periodontitis and C-reactive protein: A systematic review and meta-analysis of randomized clinical trials," *Journal of Clinical Periodontology,* vol. 50, no. 1, pp. 45-6, 10 August 2022.

[43] H. Hatahira, J. Abe, Y. Hane, et al., "Drug-induced gingival hyperplasia: a retrospective study using spontaneous reporting system databases," *Journal of Pharmaceutical Health Care and Sciences,* vol. 3, article 19, pp. 1-11, 19 July 2017.

[44] CDHO, "Hypertension in adults CDHO factsheet," 22 May 2022. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Hypertension.pdf. [Accessed 25 March 2023].

[45] CDHO, "Direct oral anticoagulants CDHO factsheet," 17 January 2022. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_DOAC.pdf. [Accessed 25 March 2023].

[46] CDHO, "Infective endocarditis CDHO factsheet," 14 June 2021. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Infective_Endocarditis.pdf. [Accessed 25 March 2023].

[47] CDHO, "Angina CDHO factsheet," 24 January 2022. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Angina.pdf. [Accessed 25 March 2023].

[48] P. Balakumar, M. Kavitha and S. Nanditha, "Cardiovascular drugs-induced oral toxicities: A murky area to be revisited and illuminated," *Pharmacological Research,* vol. 102, pp. 81-89, December 2015.

[49] L. Torpet, C. Kragelund, J. Reibel and B. Nauntofte, "Oral Adverse Drug Reactions to Cardiovascular Drugs," *Critical Reviews in Oral Biology & Medicine,* vol. 15, no. 1, January 2004.

[50] CDHO, "Heart failure CDHO factsheet," 2 June 2021. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Heart_Failure_CHF.pdf. [Accessed 25 March 2023].

[51] CDHO, "Atrial fibrillation CDHO factsheet," 17 January 2022. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Atrial_Fibrillation.pdf. [Accessed 25 March 2023].

[52] CDHO, "Post-myocardial infarction," 17 July 2021. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Post-MI.pdf. [Accessed 25 March 2023].

[53] American Dental Association, "Oral Anticoagulant and Antiplatelet Medications and Dental Procedures," 28 September 2022. [Online]. Available: https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/oral-anticoagulant-and-antiplatelet-medications-and-dental-procedures. [Accessed 23 March 2023].

[54] CDHO, "Myocardial infarction CDHO factsheet," 6 August 2019. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Myocardial_Infarction.pdf. [Accessed 25 March 2023].

[55] CDHO, "Stroke CDHO factsheet," 3 May 2022. [Online]. Available: https://www.cdho.org/Advisories/CDHO_Factsheet_Stroke.pdf. [Accessed 24 March 2023].

[56] M. Lyons, C. Smith, E. Boaden, et al., "Oral care after stroke: Where are we now?," *European Stroke Journal,* vol. 3, no. 4, pp. 347-354, December 2018.

[57] K. Lang, "Hypertension: Salt intake may affect men and women differently," Medical News Today, 13 March 2023. [Online]. Available: https://www.medicalnewstoday.com/articles/hypertension-blood-pressure-women-more-salt-sensitive-than-men. [Accessed 25 March 2023].

[58] C. Barris, J. Faulkner and E. Belin de Chantemèle, "Salt sensitivity of blood pressure in women," *Hypertension,* vol. 80, pp. 268-278, 2023.

[59] Heart and Stroke Foundation of Canada, "The DASH Diet to lower high blood pressure," 2023. [Online]. Available: https://www.heartandstroke.ca/healthy-living/healthy-eating/dash-diet. [Accessed 25 March 2023].

[60] World Health Organization, "WHO global report on sodium intake reduction," 9 March 2023. [Online]. Available: https://www.who.int/publications/i/item/9789240069985. [Accessed 25 March 2023].

[61] World Health Organization, "Massive efforts needed to reduce salt intake and protect lives," 9 March 2023. [Online]. Available: https://www.who.int/news/item/09-03-2023-massive-efforts-needed-to-reduce-salt-intake-and-protect-lives. [Accessed 25 March 2023].

[62] World Health Organization, "Sodium Country Score Card," 6 October 2022. [Online]. Available: https://extranet.who.int/nutrition/gina/en/scorecard/sodium. [Accessed 25 March 2023].

[63] E. Harris, "WHO: Nations Must Do More to Reduce Salt Consumption by 2025," *JAMA Network,* 22 March 2023.

[64] B. Huang, B. del Pozo Cruz, A. Teixeira-Pinto, et al., "Influence of poor sleep on cardiovascular disease-free life expectancy: A multi-resource-based population cohort study," *BMC Medicine,* vol. 21, article 75, pp. 1-11, 2 March 2023.

[65] S. Yuan, M. Levin, O. Titova, et al., "Sleep duration, daytime napping, and risk of peripheral artery disease: Multinational cohort and Mendelian randomization studies," *European Heart Journal Open,* vol. 3, no. 2, pp. 1-10, 2 March 2023.

[66] R. Murphy, C. Reddin, A. Rosengren, et al., "Depressive symptoms and risk of acute stroke: INTERSTROKE case-control study," *Neurology,* 8 March 2023.

[67] K. Kim, T. Kim, S. Kang, et al., "Effect of dental screening on cardiovascular risk: A nationwide cohort study," *Journal of Clinical Periodontology,* vol. 49, no. 3, pp. 251-259, 12 December 2021.

[68] S. Janket, C. Lee, M. Surakka, et al., "Oral hygiene, mouthwash usage and cardiovascular mortality during 18.8 years of follow-up," *British Dental Journal,* pp. 1-6, 23 February 2023.

[69] R. Del Pinto, D. Pietropaoli, G. Grassi, et al., "Home oral hygiene is associated with blood pressure profiles: Results of a nationwide survey in Italian pharmacies," *Journal of Clinical Periodontology,* vol. 49, no. 12, pp. 1234-1243, 12 September 2022.

[70] S. Park, S. Kim, S. Kang, et al., "Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: A population-based study from Korea," *European Heart Journal,* vol. 40, no. 14, pp. 1138-1145, 19 April 2019.

[71] AADOCR, "Study Aims to Develop a Machine Learning Model to Predict Cardiovascular Disease Using Indicators of Oral Infections," 2023. [Online]. Available: https://www.aadocr.org/about/news-reports/press-releases/study-aims-develop-machine-learning-model-predict-0. [Accessed 24 March 2023].

[72] H. Sun, Z. Wu, X. Nie and J. Bian, "Role of Endothelial Dysfunction in Cardiovascular Diseases: The Link Between Inflammation and Hydrogen Sulfide," *Frontiers in Pharmacology,* vol. 10, article 1568, pp. 1-15, 21 January 2020.

[73] M. Félétou, The Endothelium Part 1: Multiple Functions of the Endothelial Cells—Focus on Endothelium-Derived Vasoactive Mediators:, California: Morgan & Claypool Life Sciences, 2011.

[74] M. Mittal, M. Siddiqui, K. Tran, S. Reddy and A. Malik, "Reactive oxygen species in inflammation and tissue injury," *Antioxidants & Redox Signaling,* vol. 20, no. 7, pp. 1126-1167, 1 March 2014.

Client resources

Oral Health and Overall Health, ODHA Factsheet
https://odha.on.ca/wp-content/uploads/2016/08/Overall-Health.14.1-copyright.pdf

Periodontal (Gum) Disease, ODHA Factsheet
https://odha.on.ca/wp-content/uploads/2016/08/Gum-Disease.14.1-copyright.pdf

Canada's Food Guide
https://food-guide.canada.ca/en/

Additional resources

Severity and progression rate of periodontitis are associated with an increased risk of hypertension of patients attending a university clinic, Yildirim, B; Aksit, C; Mutlu, M; et al. *BMC Oral Health*, Volume 22, Article 627, December 22, 2022, p 1-9 https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-022-02637-w

The relationship between tooth loss and hypertension: A systematic review and meta-analysis, Tada, A; Tano, R; Miura, H. *Scientific Reports*, Volume 12, Article 13311, August 3, 2022, p 1-12 https://www.nature.com/articles/s41598-022-17363-0

Association between tooth loss and hypertension: A systematic review and meta-analysis, *Journal of Dentistry*, Volume 123, Article 104178, August 2022 https://www.sciencedirect.com/science/article/abs/pii/S0300571222002342

The additive effect of periodontitis with hypertension on risk of systemic disease and mortality, Larvin, H; Kang, J; Aggarwal, V; et al. *Journal of Periodontology*, Volume 93, Issue 7, April 23, 2022, p 1024-1035 https://aap.onlinelibrary.wiley.com/doi/10.1002/JPER.21-0621

Association between oral health and cardiovascular outcomes in patients with hypertension: A nationwide cohort study, Kim, J; Kim H; Jeon, J; Song, T. *Journal of Hypertension*, Volume 40, Issue 2, February 2022, p 374-381 https://frhta.org/wp-content/uploads/2022/05/Association_between_oral_health_and_cardiovascular.JHypertension2022.pdf

Tooth loss is associated with an increased risk of hypertension: A nationwide population-based cohort study, Woo, H; Chang, Y; Lee, J; Song, T. *PLoS ONE*, Volume 16, Issue 6, June 15, 2021, p 1-11 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0253257

Hypertension In Adults, CDHO Factsheet, May 22, 2022, p 1-7 https://www.cdho.org/Advisories/CDHO_Factsheet_Hypertension.pdf

Hypertension In Children & Adolescents, CDHO Factsheet, May 22, 2022, p 1-7 https://www.cdho.org/Advisories/CDHO_Factsheet_Hypertension_in_Children.pdf

Hypertension (High Blood Pressure), American Dental Association, November 1, 2022 https://www.ada.org/resources/research/science-and-research-institute/oral-health-topics/hypertension

Associations of genetic and infectious risk factors with coronary heart disease, Hodel, F; Xu, Z; Thorball, C; et al. *eLife*, Volume 12, February 14, 2023, p 1-22 https://elifesciences.org/articles/79742

Oral health and cardiometabolic disease: Understanding the relationship, King, S; Chow, C; Eberhard, J. *Internal Medicine Journal*, Volume 52, Issue 2, February 20, 2022, p 198-205 https://onlinelibrary.wiley.com/doi/10.1111/imj.15685

Oral health and atherosclerotic cardiovascular disease: A review, Gianos, E; Jackson, E; Tejpal, A; et al. *American Journal of Preventive Cardiology*, Volume 7, September 2021, p 1-7 https://www.sciencedirect.com/science/article/pii/S2666667721000349

Periodontitis and cardiovascular diseases: Consensus report, Sanz, M; Castillo, A; Jepsen, S; et al. *Journal of Clinical Periodontology*, Volume 47, Issue 3, February 3, 2020, p 268-288 https://onlinelibrary.wiley.com/doi/10.1111/jcpe.13189

Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association? Lockhart, P; Bolger, A; Papapanou, P; et al. *Circulation*, Volume 125, Issue 20, April 18, 2012, p 2520-2544 https://www.ahajournals.org/doi/10.1161/CIR.0b013e31825719f3

Periodontal therapy for primary or secondary prevention of cardiovascular disease in people with periodontitis, Ye, Z; Cao, Y; Miao, C: et al. *Cochrane Database of Systematic Reviews*, Issue 10, October 4, 2022 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009197.pub5/full

Regular dental visits, periodontitis, tooth loss, and atherosclerosis: The Ohasama study, Yamada, S; Komiyama, T; Ohi, T; et al. *Journal of Periodontology Research*, Volume 57, Issue 3, April 6, 2022, p 615-622 https://onlinelibrary.wiley.com/doi/10.1111/jre.12990

Association between myocardial infarction and periodontitis: A meta-analysis of case-control studies, Shi, Q; Zhang, B; Huo, N; et al. *Frontiers in Physiology*, Volume 7, Article 519, November 4, 2016, p 1-12 https://www.frontiersin.org/articles/10.3389/fphys.2016.00519/full

Association between periodontal care and hospitalization with acute myocardial infarction, Nalliah, R; Basu, T; Change, C. *Journal of the American Dental Association*, Volume 153, Issue 8, August 2022, p 776-786 https://jada.ada.org/article/S0002-8177(22)00087-3/fulltext

Is poor oral health a risk marker for incident cardiovascular disease hospitalisation and all-cause mortality? Findings from 172 630 participants from the prospective 45 and Up Study, Joshy, G; Arora, M; Korda, R; Chalmers, J; Banks, E. *BMJ Open*, Volume 6, Issue 8, p 1-10 https://bmjopen.bmj.com/content/6/8/e012386

Periodontitis is associated with heart failure: A population-based study (NHANES III), Yan, Y; Mao, M; Li, Y; et al. *Frontiers in Physiology*, Volume 13, Article 854607, April 20, 2022, p 1-8 https://www.frontiersin.org/articles/10.3389/fphys.2022.854606/full

Relationship between periodontitis and atrial fibrosis in atrial fibrillation: Histological evaluation of left atrial appendages, Miyauchi, S; Nishi, H; Ouhara, K; et al. *JACC: Clinical Electrophysiology*, Volume 9, Issue 1, January 2023, p 43-53 https://www.sciencedirect.com/science/article/abs/pii/S2405500X22007290

Association between oral health and atrial fibrillation: A systematic review, Leelapatana, P; Limpuangthip, N. *Heliyon*, Volume 8, Issue 3, March 23, 2022, p 1-9 https://www.cell.com/heliyon/fulltext/S2405-8440(22)00449-2

Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*, Kozarov, E; Dorn, B; Shelburne, C; et al. *Arteriosclerosis, Thrombosis, and Vascular Biology*, Volume 25, January 20, 2005, p e17-e18 https://www.ahajournals.org/doi/full/10.1161/01.ATV.0000155018.67835.1a

The oral microbiota in valvular heart disease: Current knowledge and future directions, Neculae, E; Gosav, E; Valasciuc, E; et al. *Life*, Volume 13, Issue 1, January 8, 2023, p 1-20 https://www.mdpi.com/2075-1729/13/1/182

The oral microbiota and cardiometabolic health: A comprehensive review and emerging insights, Li, Y; Zhu, M; Liu, Y; et al. *Frontiers in Immunology*, Volume 13, November 18, 2022, p 1-15 https://www.frontiersin.org/articles/10.3389/fimmu.2022.1010368/full

Oral microbiome is associated with incident hypertension among postmenopausal women, LaMonte, M; Gordon, J; Diaz-Moreno, P; et al. *Journal of the American Heart Association*, Volume 11, Issue 6, March 2, 2022, p 1-43 https://www.ahajournals.org/doi/10.1161/JAHA.121.021930

Oral bacterial signatures in cerebral thrombi of patients with acute ischemic stroke treated with thrombectomy, Patrakka, O; Pienimäki, J; Tuomisto, S; et al. *Journal of the American Heart Association,* Volume 8, Issue 11, May 23, 2019, p 1-7 https://www.ahajournals.org/doi/10.1161/JAHA.119.012330

The role of natural salivary defences in maintaining a healthy oral microbiota, Pedersen, A; Belstrøm, D. *Journal of Dentistry*, Volume 80, Supplement 1, January 2019, p S3-S12 https://www.sciencedirect.com/science/article/pii/S030057121830335X

Roles of oral infections in the pathomechanism of atherosclerosis, Aarabi, G Heydecke, G; Seedorf, U. *International Journal of Molecular Science*, Volume 19, Issue 7, July 6, 2018, p 1-12 https://www.mdpi.com/1422-0067/19/7/1978

Presence of periodontal pathogenic bacteria in blood of patients with coronary artery disease, Corredor, Z; Suarex-Molina, A; Fong, C; et al. *Scientific Reports*, Volume 12, Article 1241, January 24, 2022, p 1-11 https://www.nature.com/articles/s41598-022-05337-1

Efficacy of non-surgical periodontal treatment on patients with coronary artery disease: A meta-analysis of randomized controlled trials, Liu, C; Shi, F; Li, W; Chen, J. *Med, Oral Patol, Oral Cir Bucal*, Volume 27, Issue 6, November 2022, p e578-e587 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9648645/

Effect of periodontal treatments on blood pressure, Luo, Y; Ye, H; Liu, W; et al. *Cochrane Database of Systematic Reviews*, Issue 12, December 12, 2021 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009409.pub2/full

Periodontal treatment on patients with cardiovascular disease: Systematic review and meta-analysis, Roca-Millan, E; González-Navarro, B; Sabater-Recolons, M; et al. *Med Oral Patol Oral Cir Bucal*, Volume 23, Issue 6, November 2018, p e681-e690 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6261003/

Is periodontal therapy an effective treatment modality for preventing or managing cardiovascular disease in patients with periodontitis? Goyal, L; Gupta, S; Dewan, M; Singla, M. *Evidence-based Dentistry*, Volume 24, March 8, 2023, p 32-34 https://www.nature.com/articles/s41432-023-00868-6

Treatment of periodontitis and C-reactive protein: A systematic review and meta-analysis of randomized clinical trials, Luthra, S; Orlandi, Marco, Hussain, Sy; et al. *Journal of Clinical Periodontology*, Volume 50, Issue 1, August 10, 2022, p 45-60 https://onlinelibrary.wiley.com/doi/full/10.1111/jcpe.13709

Oral adverse drug reactions to cardiovascular drugs, Torpet, L; Kragelund, C; Reibel, J; Nauntofte, B. *Critical Reviews in Oral Biology & Medicine*, Volume 15, Issue 1, January 2004, p 28-46 https://journals.sagepub.com/doi/10.1177/154411130401500104

Oral care after stroke: Where are we now? Lyons, M; Smith, C; Boaden, E; et al. *European Stroke Journal*, Volume 3, Issue 4, December 2018, p 347-354 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6571511/

Direct Oral Anticoagulants, CDHO Factsheet, January 17, 2022, p 1-4 https://www.cdho.org/Advisories/CDHO_Factsheet_DOAC.pdf

Angina, CDHO Factsheet, June 24, 2022, p 1-5 https://www.cdho.org/Advisories/CDHO_Factsheet_Angina.pdf

Atrial Fibrillation, CDHO Factsheet, January 17, 2022, p 1-5 https://www.cdho.org/Advisories/CDHO_Factsheet_Atrial_Fibrillation.pdf

Heart Failure, CDHO Factsheet, June 2, 2021, p 1-5 https://www.cdho.org/Advisories/CDHO_Factsheet_Heart_Failure_CHF.pdf

Infective Endocarditis, CDHO Factsheet, June 14, 2021, p 1-8 https://www.cdho.org/Advisories/CDHO_Factsheet_Infective_Endocarditis.pdf

Myocardial infarction, CDHO Factsheet, September 6, 2019, p 1-4
https://www.cdho.org/Advisories/CDHO_Factsheet_Myocardial_Infarction.pdf

Post-Myocardial Infarction, CDHO Factsheet, July 17, 2021, p 1-6
https://www.cdho.org/Advisories/CDHO_Factsheet_Post-MI.pdf

Stroke, CDHO Factsheet, May 3, 2022, p 1-6
https://www.cdho.org/Advisories/CDHO_Factsheet_Stroke.pdf

Effect of dental screening on cardiovascular risk: A nationwide cohort study, Kim, K; Kim T; Kang, S; et al. *Journal of Clinical Periodontology*, Volume 49, Issue 3, December 12, 2021, p 251-259 https://onlinelibrary.wiley.com/doi/10.1111/jcpe.13584

Oral hygiene, mouthwash usage and cardiovascular mortality during 18.8 years of follow-up, Janket, S; Lee, C; Surakka, M; et al. *British Dental Journal*, February 3, 2023, p 1-6 https://www.nature.com/articles/s41415-023-5507-4

Home oral hygiene is associated with blood pressure profiles: Results of a nationwide survey in Italian pharmacies, Del Pinto, R; Pietropaoli, D; Grassi, G; et al. *Journal of Clinical Periodontology*, Volume 49, Issue 12, September 12, 2022, p 1234-1243
https://onlinelibrary.wiley.com/doi/10.1111/jcpe.13720

Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: A population-based study from Korea, Park, S; Kim, S; Kang, S; et al. *European Heart Journal,* Volume 40, Issue 14, April 17, 2019, p 1138-1145
https://academic.oup.com/eurheartj/article/40/14/1138/5251907