

Cardiovascular prevention starts from your mouth

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This editorial refers to 'Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea', by S.-Y. Park et al., doi:10.1093/eurheartj/ehy836.

Atherosclerosis remains the leading cause of cardiovascular disease worldwide and recent clinical evidence has confirmed that inflammation plays a significant role in its complications.^{1,2} Diseases characterized by a chronic inflammatory exposure (including rheumatoid arthritis, psoriasis, oral inflammatory diseases, chronic bowel diseases, etc.) have been associated with raised risk of future cardiovascular events, and have been studied to explore the potential impact of anti-inflammatory drugs or procedures on mitigating the cardiovascular risk.³ The ability to modulate inflammation in these conditions has also enabled identification of inflammatory pathways potentially involved in the regulation of vascular homeostasis. The association between parameters of poor oral health and risk of cardiovascular diseases has been repeatedly reported by observational (cross-sectional, case controls, and prospective) studies in humans, leading to the inclusion of periodontitis (a common oral inflammatory disease) in the group of potential conditions increasing the risk of cardiovascular disease in the most recent European Guidelines for cardiovascular disease prevention.⁴ The interest around the potential link between oral health and cardiovascular disease is explained by its potential benefits in term of cardiovascular disease prevention. Indeed, oral diseases are highly prevalent in the general population, collectively affecting 3.9 billion people worldwide.⁵ This prevalence is significantly higher than other common cardiovascular risk factors (i.e. diabetes) and if a causal link with atherosclerosis could be demonstrated, the proportion of individuals in the general population who might obtain cardiovascular benefits from improved oral health could be substantial, with a significant reduction of the costs for the public health systems.

In this issue of the *European Heart Journal*, Kang et al. report the results of a large, prospective, population-based study exploring the potential influence of oral health care on the future risk of

cardiovascular disease.⁶ Using data from the National Health Insurance System-National Health Screening Cohort, including almost the entire population in Korea, the authors documented that an increased number of dental caries, the presence of periodontitis, and a greater loss of teeth were associated with an increased risk of future major cardiovascular events (MACEs), including cardiovascular death, acute myocardial infarction, heart failure, and stroke. Importantly, frequent tooth brushing and regular dental visits were associated with a lower cardiovascular disease risk, and mitigated the risk of cardiovascular events in participants with oral diseases. While, the association between periodontitis and adverse cardiovascular events lost statistical significance after multivariable adjustments, including age, hypertension, diabetes, and tobacco smoking, measures of dental caries and tooth loss remained significantly associated with the risk of MACEs in the fully adjusted model. Based on these results, the authors concluded that oral health promotion strategies (i.e. better dental hygiene behaviour) could modify the cardiovascular risk associated with poor oral health.

The results by Kang et al. confirm previous studies suggesting a potential impact of oral inflammatory diseases on the risk of cardiovascular events, over and above the contribution of traditional cardiovascular risk factors.⁷ They also provide clinical evidence for a potential benefit in cardiovascular protection achieved by the simple adoption of better oral health behaviours in a large prospective study. This is important as current guidelines recognize the general lack of knowledge on the potential cardiovascular benefits obtained with active treatment of oral health diseases.⁴

The biological pathways accounting for the results presented by Kang et al. remain to be clarified. We have previously documented that periodontitis and an intensive treatment regimen able to improve gingival health can alter systemic inflammation, and have profound effects on endothelial cell function and biology.⁸ More recently, we confirmed that the same treatment improves metabolic control and endothelial function, and prevents renal deterioration in patients with type 2 diabetes.⁹ Based on these results, and considering the elevated systemic inflammatory burden commonly observed

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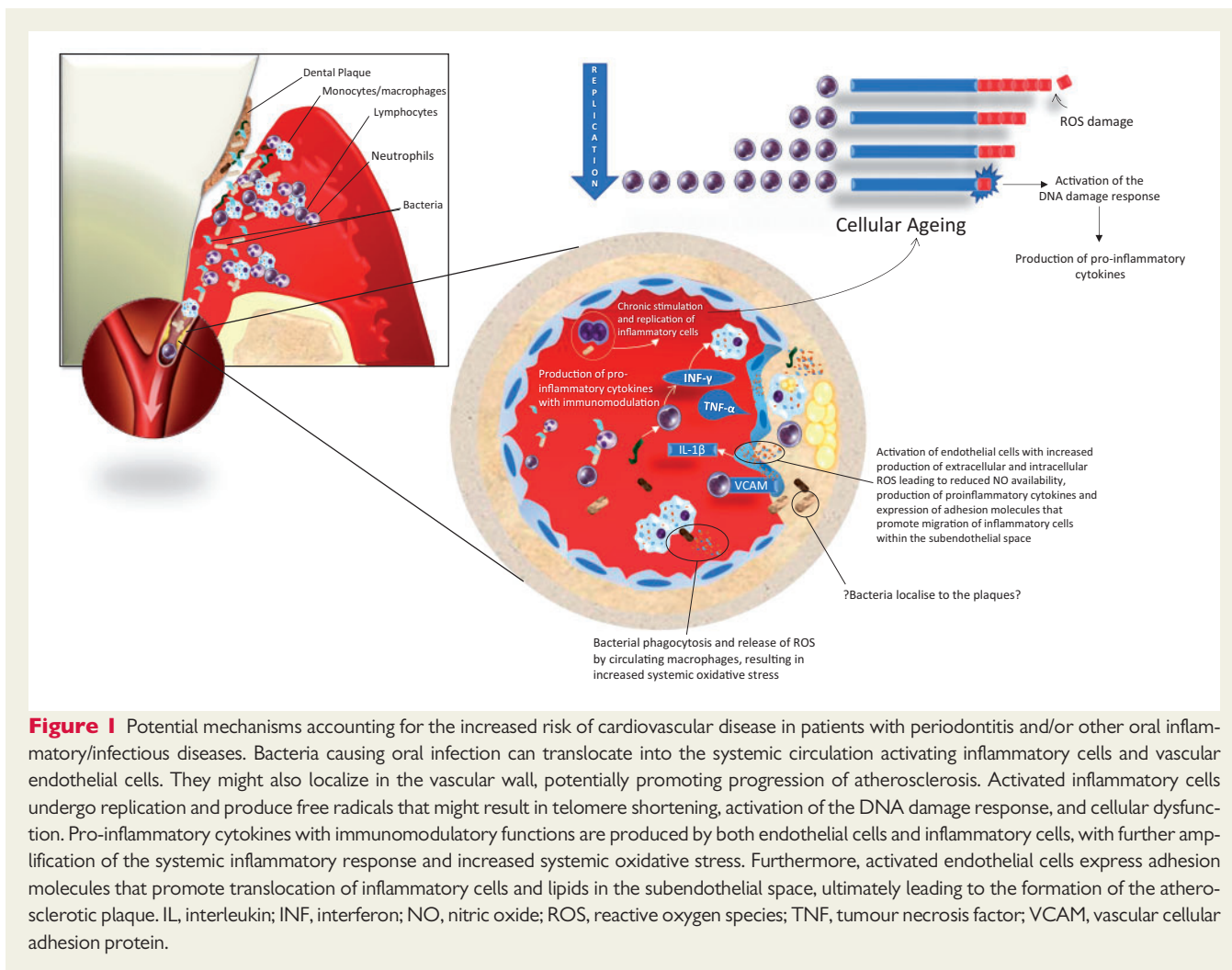


Figure 1 Potential mechanisms accounting for the increased risk of cardiovascular disease in patients with periodontitis and/or other oral inflammatory/infectious diseases. Bacteria causing oral infection can translocate into the systemic circulation activating inflammatory cells and vascular endothelial cells. They might also localize in the vascular wall, potentially promoting progression of atherosclerosis. Activated inflammatory cells undergo replication and produce free radicals that might result in telomere shortening, activation of the DNA damage response, and cellular dysfunction. Pro-inflammatory cytokines with immunomodulatory functions are produced by both endothelial cells and inflammatory cells, with further amplification of the systemic inflammatory response and increased systemic oxidative stress. Furthermore, activated endothelial cells express adhesion molecules that promote translocation of inflammatory cells and lipids in the subendothelial space, ultimately leading to the formation of the atherosclerotic plaque. IL, interleukin; INF, interferon; NO, nitric oxide; ROS, reactive oxygen species; TNF, tumour necrosis factor; VCAM, vascular cellular adhesion protein.

in patients with diabetes and oral diseases, it could be speculated that the systemic benefits obtained with improved oral health could depend on reduced exposure to chronic systemic inflammation (Figure 1). As highlighted by Kang *et al.*, this hypothesis is in keeping with the results of the Canakinumab Antiinflammatory Thrombosis Outcome Study (also known as CANTOS trial), showing that reduction of systemic inflammation reduces the risk of cardiovascular events and mortality in patients with established atherosclerosis.¹⁰ However, while in patients with diabetes we were able to document a significant reduction of C-reactive protein after intensive periodontal treatment compared to the control group, we could not find any associations between changes of this and other inflammatory markers and the improved endothelial function.^{8,9} The results by Kang *et al.* somewhat confirm that, over and above inflammation, there might be other factors accounting for the link between oral diseases and cardiovascular health. Indeed, dental caries are commonly associated with a lower systemic inflammatory exposure compared to periodontal diseases and, despite this, they had a stronger association with adverse cardiovascular events. The systemic inflammatory response in patients suffering from oral diseases is thought to depend on the translocation of pathogenic bacteria from the oral cavity to

the systemic circulation.⁷ Significant interest in recent years has focused on microbiota–host interactions, as accumulating evidence has revealed that the microbiota might play an important role in cardiovascular diseases. Changes in the composition of the oral microbiota, referred to as dysbiosis, have been suggested as potential causes of oral diseases¹¹ and oral bacteria have been isolated from atherosclerotic plaques (Figure 1).¹² Thus, a dysbiosis that promotes the evolution of oral disease might also contribute to the development of atherosclerosis with mechanisms that are not reflected necessarily by the levels of C-reactive protein. The role of oral bacteria as central mediators of the link between oral and cardiovascular diseases might also account for the benefits of frequent tooth brushing and regular dental visits described by Kang *et al.* Indeed, these procedures are associated with better control of the microbial plaque.

The relationship between oral health and cardiovascular disease might also lie in the increase of systemic oxidative stress (Figure 1). This might affect the risk of cardiovascular events and progression of oral disease by altering the function of immune-inflammatory cells by two separate mechanisms. Firstly, while intracellular oxidative stress might reduce nitric oxide availability, thus promoting endothelial dysfunction, it might also modify the pattern of cytokines

produced by immune-inflammatory cells, reducing their capacity to contrast the bacterial aggression to the oral cavity.¹³ We recently reported that the production of mitochondrial reactive oxygen species in immune-inflammatory cells is influenced by periodontal treatment, represents the strongest predictor of the changes in endothelial function, and is accompanied by changes in the production of cytokines with an essential role in the regulation of the innate as well as adaptive immunity.¹⁴ Secondly, chronic activation of the immune-inflammatory cells and exposure to elevated levels of oxidative stress might lead to their exhaustion, ultimately resulting in cellular ageing (Figure 1). We have documented that patients with chronic periodontitis have shorter leukocyte telomere length, and that the size of telomeres is directly related to circulating levels of oxidative stress and the severity of the oral diseases.^{15,16} In turn, telomere shortening has been associated with cardiovascular disease,¹⁷ and cells with critically short telomeres might favour progression of the oral disease, as they produce higher levels of proinflammatory cytokines and lose their capacity to respond effectively to bacterial aggressions.

In summary, the study by Kang *et al.* has the merit of confirming the strong link between oral health and the risk of cardiovascular diseases. For the first time, it also provides evidence of the potential impact of better dental hygiene on the future risk of cardiovascular events/mortality. While large clinical trials assessing the impact of better oral health on hard cardiovascular outcomes are still lacking and the mechanisms accounting for the potential reduction of cardiovascular disease risk achieved with better oral health remain largely unknown, this manuscript adds to our knowledge of the role of poor oral health in cardiovascular diseases. Given that periodontal diseases are the commonest form of inflammatory/infectious diseases worldwide, the public health benefits of promoting oral health are potentially large.

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