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Associations between tooth loss and prognostic biomarkers and the risk for cardiovascular events in patients with stable coronary heart disease☆,☆☆

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ABSTRACT

Background: Underlying mechanisms behind the hypothesized relationship between periodontal disease (PD) and coronary heart disease (CHD) have been insufficiently explored. We evaluated associations between self-reported tooth loss- a marker of PD- and prognostic biomarkers in 15,456 (97%) patients with stable CHD in the global STABILITY trial.

Methods and results: Baseline blood samples were obtained and patients reported their number of teeth according to the following tooth loss levels: "26–32 (All)" [lowest level], "20–25", "15–19", "1–14", and "No Teeth" [highest level]. Linear and Cox regression models assessed associations between tooth loss levels and biomarker levels, and the relationship between tooth loss levels and outcomes, respectively.

After multivariable adjustment, the relative biomarker increase between the highest and the lowest tooth loss level was: high-sensitivity C-reactive protein 1.21 (95% confidence interval, 1.14–1.29), interleukin 6 1.14 (1.10–1.18), lipoprotein-associated phospholipase A_2 activity 1.05 (1.03–1.06), growth differentiation factor 15 1.11 (1.08–1.14), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) 1.18 (1.11–1.25). No association was detected for high-sensitivity troponin T 1.02 (0.98–1.05). Some attenuation of the relationship between tooth loss and outcomes resulted from the addition of biomarkers to the multivariable analysis, of which NT-proBNP had the biggest impact.

Conclusions: A graded and independent association between tooth loss and several prognostic biomarkers was observed, suggesting that tooth loss and its underlying mechanisms may be involved in multiple pathophysiological pathways also implicated in the development and prognosis of CHD. The association between tooth loss

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and cardiovascular death and stroke persisted despite comprehensive adjustment including prognostic biomarkers.

Clinical trial registration: www.clinicaltrials.gov; NCT00799903.

1. Introduction

There is a growing body of evidence favouring an independent association between oral health and coronary heart disease (CHD) [1–3]. We have recently reported an association between tooth loss and cardiovascular (CV) outcomes, but not myocardial infarction (MI), in a chronic CHD population [4]. In the literature, the hypothesized relationship between dental disease and CV disease is often attributed to deleterious effects of periodontal disease (PD), a highly prevalent chronic inflammatory condition ranging from early gingivitis to end-stage tooth loss, on the atherosclerotic process but specific mechanisms remain elusive and debated [5].

Pathophysiological information on multiple aspects of etiology and progression of CV disease is reflected by several biomarkers, many of which also have robust capabilities of predicting prognosis [6–11]. Thus, associations between markers of PD, biomarkers, and CV outcomes could provide further insights about possible mechanisms connecting PD and CV disease. However, such existing observations mainly stem from smaller populations and are limited to selected inflammatory markers such as C-reactive protein and interleukin-6 [12,13], whereas reported associations with other important biomarkers are either scarce or non-existent.

We evaluated associations between self-reported tooth loss, a marker of oral disease and PD, and a wide range of prognostic biomarkers, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), lipoprotein-associated phospholipase A_2 activity (Lp-PLA_2), growth differentiation factor 15 (GDF-15), high-sensitivity troponin T (hs-Troponin T) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) in a large global CHD population. Further, we assessed the influence of these biomarkers on the ability of self-reported tooth loss to predict CV outcomes.

2. Methods

2.1. Study population

The STabilization of Atherosclerotic plaque By Initiation of darapLadIb TherapY (STABILITY) study evaluated the efficacy of darapladib, an oral inhibitor of lipoprotein-associated phospholipase A_2 activity (Lp-PLA_2) compared to placebo in addition to optimal medical treatment in 15,828 participants from 39 countries with stable CHD, defined as prior myocardial infarction (MI), prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), or multivessel CHD without revascularization. At least one additional enrichment criterion was required: age ≥ 60 years; diabetes mellitus requiring pharmacotherapy; high-density lipoprotein cholesterol <1.03 mmol/L; current or previous smoker defined as ≥5 cigarettes per day on average; moderate renal dysfunction (estimated glomerular filtration rate ≥ 30 and <60 mL/min/1.73 m^2 or urine albumin:creatinine ratio ≥ 30 mg albumin/g creatinine); or polyvascular disease (co-existing disease in at least two arterial territories). Patients with an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 were excluded [14]. After a median follow-up of 3.7 years, no difference in major adverse cardiovascular events (MACE, i.e. first occurrence of CV death, myocardial infarction or stroke) was observed for patients randomized to darapladib compared to placebo [15]. The ethics committees of each participating country approved the study and all patients provided written informed consent prior to inclusion. The STABILITY trial was performed in accordance with the Declaration of Helsinki.

2.2. Data collection

At baseline, 15,456 (97%) patients reported their number of teeth according to the following categories: "26–32 (All teeth)", "20–25", "15–19", "1–14", and "No Teeth". For the purposes of this report, these categories are termed tooth loss levels with 26–32 teeth corresponding to the lowest level and no teeth, the highest level.

Blood samples for routine laboratory tests and storage for later analyses were obtained in all 15,456 patients at baseline and prognostic biomarker analyses were performed in the majority of patients. Plasma aliquots were stored at −70 °C until biochemical analysis. All routine biochemical and hs-CRP analyses were performed at a central laboratory with standardized methods (Quest Diagnostics Clinical Laboratories, Inc., Valencia, California, USA). Plasma concentrations of hs-CRP were analyzed using a particle-enhanced immunonephelometry assay, *CardioPhase©* hsCRP, Siemens Healthcare. Plasma concentrations of high-sensitivity IL-6 were analyzed using an ELISA technique, R&D Systems Inc., Minneapolis, MN, U.S.A. Lp-PLA_2 activity was measured in an automated enzyme assay system (PLAC® Test for Lp-PLA_2 Activity, diaDexus, San Francisco, CA, USA). The other biomarker assays were performed at the UCR Laboratory at Uppsala University, Uppsala, Sweden, GDF-15 was measured with the GDF-15 precommercial assay (Roche Diagnostics, Penzberg, Germany), composed of a monoclonal mouse antibody for capture and a monoclonal mouse antibody fragment, [F(ab′)2], for detection in a sandwich assay format. Detection was based on an electrochemiluminescence immunoassay using a ruthenium (II) complex label. Levels of hs-Troponin T and NT-proBNP were also determined by electrochemiluminescence (Roche Diagnostics, Penzberg, Germany). The Cobas Analytics e601 was used for the Roche immunoassays.

2.3. Statistical analysis

Baseline variables are presented as mean, standard deviation and percentages. Baseline biomarker levels are presented as median and interquartile range. Baseline biomarker levels by tooth loss level were compared using the Kruskal-Wallis tests.

To determine associations between tooth loss levels and biomarker levels, each biomarker was modelled as a function of tooth loss level (five levels). All biomarkers were analyzed on a log-transformed scale using linear models. Geometric mean ratios are presented with 95% confidence intervals (CI) with the lowest tooth loss level (26–32 teeth) as reference, and according to three adjustment models. Model 1 adjusted for randomized treatment. Model 2 adjusted for Model 1 and prior MI, prior coronary revascularization, multi-vessel CHD, age, sex, geographic region, diabetes mellitus, hypertension, renal dysfunction, body mass index, smoking (current, former or never), systolic blood pressure and polyvascular disease. Model 3 adjusted for Model 2 and estimated glomerular filtration rate (according to The Chronic Kidney Disease Epidemiology Collaboration equation, replacing significant renal dysfunction) [16], hemoglobin, white blood cells, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides. Cox proportional hazards models were used to calculate hazard ratios for MACE, CV death and stroke in relation to tooth loss levels, adjusting for biomarkers in addition to a previously reported multivariable model [4], co-variables of which are also listed in Table 3. In these models, all biomarkers except Lp-PLA_2 activity were added after log-transformation. The association between tooth loss and MI has previously been found to be absent in this cohort and was not re-analyzed in the present analysis.

A p-value <0.05 was considered statistically significant in all analyses. Analyses were performed at the Uppsala Clinical Research Center, Uppsala, Sweden using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Baseline characteristics and associations with biomarkers

Patients with higher tooth loss levels were older, were more likely to be female and had a greater CV risk factor burden, particularly a higher prevalence of smoking, diabetes mellitus, hypertension and impaired renal function compared to those with lower tooth loss levels (Table 1). Patients with more tooth loss had progressively higher baseline levels of hs-CRP, IL-6, Lp-PLA_2 activity, GDF-15, hs-Troponin T and NT-proBNP (Table 2). As demonstrated in Fig. 1, higher tooth loss levels were associated with progressively greater relative increases for all prognostic biomarkers in relation to the lowest tooth less level in Model 1. After multivariable adjustment the association remained statistically significant for all biomarkers, except for hs-Troponin T.

3.2. Tooth loss and outcomes

Table 3 demonstrates the association between a one-level increase in tooth loss and the risk of MACE, CV death and stroke according to the three adjustment models after a median follow-up of 3.7 years. The data up until Model 2 have been previously presented [4] showing a relative risk increase of 1.06, 1.17 and 1.14 for MACE, CV death and for stroke, respectively, for every one-level increase in tooth loss. The

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