Low levels of antibodies for the oral bacterium *Tannerella forsythia* predict cardiovascular disease mortality in men with myocardial infarction: A prospective cohort study

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**ABSTRACT**

Antibody levels to periodontal pathogens in prediction of cardiovascular disease (CVD) mortality were explored using data from a health survey in Oslo in 2000 (Oslo II-study) with 12 1/2 years follow-up. IgG antibodies to four common periodontal pathogens; *Tannerella forsythia* (TF), *Porphyromonas gingivalis* (PG), and *Treponema denticola* (TD) all termed collectively the “red complex”, and *Aggregatibacter actinomycetemcomitans* (AA) were analysed. The study sample consisted of 1172 men drawn from a cohort of 6,530 men who participated in the Oslo II-study, where they provided information on medical and dental history. Of the study sample, 548 men had reported prior myocardial infarction (MI) at baseline whereas the remaining 624 men were randomly drawn from the ostensibly healthy participants for comparative analyses. Dental anamnestic information included tooth extractions and oral infections. An inverse relation was found for trend by the quartile risk level of TF predicting CVD mortality, p-value for trend = 0.017. Comparison of the first to fourth quartile of TF antibodies resulted in hazard ratio (HR) = 1.82, 95% confidence interval 1.12–2.94, p = 0.015, adjusted for age, education, diabetes, daily smoking, and systolic blood pressure. Specificity comparing decile 1 to deciles 2–10 of TF predicting mortality was 92.3%. We found an increased HR by low levels of antibodies to the bacterium *T. forsythia* predicting CVD mortality in a 12 ½ years follow-up in persons who had experienced an MI but not among non-MI men. This novel finding constitutes a plausible causal link between oral infections and CVD mortality.

**Introduction**

Many bacteria have been identified in advanced “chronic” periodontal disease but three bacteria are commonly identified and are jointly termed the ‘Red complex’ [1–3]. The latter comprises the strict anaerobic bacteria *Tannerella forsythia* (TF), *Porphyromonas gingivalis* (PG), and *Treponema denticola* (TD). These bacteria act in symbiosis under the progression of the infection through their production of several virulence factors and they possess the ability to evade host reactions resulting in soft and hard tissue destruction in the oral cavity [4–8]. Their numbers increase with increasing periodontal pocket depth. The facultative anaerobic *Aggregatibacter actinomycetemcomitans* (AA) is associated with gingivitis and localized periodontitis (juvenile periodontitis) [9,10].

Multiple pathways for exploring and linking periodontal disease to cardiovascular disease (CVD) and atherosclerosis, in particular, have been published [4,6,7,11–19]. Both conditions are closely related to immunologic responses and inflammation. The exact mechanisms linking the two disorders have, however, not been firmly established, but several studies during the last decades provide evidence for an association between oral microbiota and CVD. Examples are DeStafano et al. who found an increased risk of atherosclerotic plaque formation associated with dental disease in 9760 patients over a 14 years follow-up [11], and in a case-control study Mattila et al. showed an association between periodontal disease and heart disease [12].

Periodontitis is well described and classified [20]. Periodontitis and other oral infections of dental origin in various stages occur in millions of people around the world [21]. It has been estimated by WHO that...
5–15% of the world’s population suffer from chronic periodontitis and juvenile periodontitis occur in about 2% of youths. Dental caries in industrialized countries affect approximately 60–90% of schoolchildren and the vast majority of adults. However, there are differences between populations. Bacterial DNA of more than 700 bacteria has been identified in the mouth but approximately 35% have not been possible to cultivate [22]. Several dental procedures may cause bacteriaemia [23,24]. Exposure to oral bacterial infections may occur at an early age in deciduous teeth with severe caries and pulpal exposure to oral bacteria. Juvenile periodontitis occurs in some young people. Hence, oral infections may occur at an early age and expose individuals over many years [24,25]. The close proximity of the periodontal bacterial infection to the bloodstream makes it highly plausible that bacteria themselves or bacterial products spread to distant sites in the cardiovascular system [26–29]. In fact, oral bacteria or their DNA have been identified in atheromas, heart valves, and arterial walls [16,30–39]. The first line of defence in these sites is the macrophages that are involved in the process of autophagy in bacterial infections [4]. Bacterial products such as lipopolysaccharides (LPSs) and increased low-density lipoprotein (LDL) accumulate in atheromas, initiating the transfer of macrophages into atheromas and their transformation into foam cells when absorbing LDL [7]. Andriankaja used indirect immunofluorescence microscopy with species-specific polyclonal and monoclonal serodiagnostic reagents when isolating six periodontal pathogens and assessing the odds of having a myocardial infarction (MI) in 1,060 men and women [14]. They found Prevotella intermedia and T. forsythia to be significantly associated with MI, OR = 1.40 (95% confidence interval (CI) 1.02–1.92) in adjusted analyses. In addition, three or more bacteria present in periodontal pockets gave an increased risk of MI, OR = 2.01 (95% CI 1.31–3.08).

The hypothesis

We hypothesize that anaerobe oral bacteria metastasize infection into the cardiovascular system as observed by IgG antibody levels. Using the Oslo II-cohort, we want in this sub-study to estimate the prediction for CVD mortality over 12 ½ years of follow-up by level of bacterial IgG antibodies to PG, TD, TF, and AA in men with a history of myocardial infarction (MI) versus men with no known history of myocardial infarction (non-MI). Knowledge of antibody levels to oral bacteria may provide important support to an etiologic explanation of the incidence and mortality of myocardial infarction related to oral infections and lead to the development of preventive measures such as a diagnostic test and a vaccine.

Evaluation of the hypothesis

The hypothesis was tested as follows: In 2000 the health survey named the Oslo II-study, a follow-up study of men invited to the Oslo Study of 1972/73 was undertaken [40–42]. Men of this cohort living in Oslo or in the surrounding county Akershus were invited to attend (n = 12,764). After screening 55 men withdrew and results from 6,530 participating men aged 48–77 years are eligible for analyses. At the screening, the men filled in a detailed questionnaire on medical history, oral health, medication, health service use, food- and drinking habits, physical activity, smoking, stress, and mental health. Oral health was defined according to the number, and cause of tooth extractions and current oral infections. Height, weight, waist, hip, and blood pressure were recorded (41). Blood samples were drawn for total cholesterol, HDL-C, glucose in the non-fasting state, and triglycerides analyses. EDTA-blood was stored at the HUNT biobank, Levanger, Norway, and the remaining serum after analyses were frozen and stored at −80 °C at the Norwegian Institute for Public Health, Oslo, Norway.

A study sample of 1172 men was drawn from the Oslo II cohort to assess prospectively the association between antibodies to four oral bacteria and mortality in a 12 ½ – years follow-up (42). The study sample consisted of 548 men who had reported a history of myocardial infarction at baseline in 2000 and 624 men randomly selected from the ostensibly healthy men in the cohort. All men had attended both health screenings and had hs-CRP measured. All procedures performed were in accordance with the ethical standards of the Norwegian institutional and national research committee REK (Helse Sør-øst) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The SPSS random generator program was used in selecting healthy subjects.

The serum samples were analysed for IgG antibodies to the oral bacteria TF, PG, TD, and AA by the ELISA method. The ELISA and IgG antibody assay used in the Oslo II-study have previously been described [42]. In short, bacteria were cultivated anaerobically at the Institute for Oral Biology, Dental faculty, University of Oslo. The ELISA was performed at the Norwegian Institute for Public Health. ELISA plates were coated with the bacterial antigen at a concentration of 5 µg protein of each of the bacteria to capture serum antibodies. Then each well was incubated overnight with 100 µl solution. Thereafter the coated wells were stored for up to 14 days at 4 °C. The human serum calibrator was diluted to 1/40, 1/80, 1/160, 1/320, 1/640, 1/1280, and 1/2560. The samples were diluted to 1/160, 1/320, 1/640, and the 170 first were also diluted to 1/80. To the washed plates were added samples or serum calibrator. These were then incubated for 2 h at room temperature. After washing, conjugated secondary antibody was added and the plates were incubated at room temperature for another 2 h. The secondary antibody was Polyclonal Rabbit Anti Human IgG/AP, D0336, 1:1000 dilution. Into each well was pipetted one hundred microliter substrate. The colour development was registered by optical density (OD) and the result was recorded as a percentage of the serum calibrator. Sample dilution curves were compared for deviation from parallelism. Mean values were used unless large deviations were observed and then median values were chosen. For more details see publication [42].

The covariates used in the analyses were selected according to known predictors for CVD and periodontal infection namely age, daily smoking, education and diabetes, which are common to oral health and CVD and systolic blood pressure, an important predictor of CVD, for prediction analyses and to adjust for confounding. In addition, health service utilization and medication use were reported. Hs-CRP was analysed in the serum samples in 2004 at the same time as the antibody analyses. Missing data were limited. The outcome during follow-up was CVD mortality. All Norwegians have a personal identification number and this was used in the matching of study participants to the Norwegian Cause of Death Registry which provides complete follow-up with regard to date and cause of death according to ICD-10 codes and I21 to I99 defines all CVD diagnoses used in this study. Mortality data were provided by Statistics Norway, and the mortality information was given in one linkage after 12 ½ years follow-up with the last date of follow-up 31.12.2012. Baseline characteristics are presented by mean and standard deviations (SD) or number and percentage. Differences between characteristics of men with or without a history of MI were examined by t-test for equality of means of independent groups for continuous variables or by Fisher’s Exact Test for dichotomous variables, two-sided test values only. The antibody variables were analyzed both as observed values, by ln-transformation due to their skewed distribution, stratified by quartile values (quartiles), and tested for correlation by the Pearson statistic. The quartiles were used on an ordinal scale applying the Pearson statistic. Mean values were used unless large deviations were observed and then median values were chosen. For more details see publication [42].
The mean, SD, minimum and maximum values, and quartile values of the antibodies towards the four bacteria according to the ELISA IgG results are shown in Table 1. The highest maximum IgG values were against PG (8,710) for MI and 5,299 for non-MI, and the lowest were those against TD with 2,166 for MI and 1,204 for non-MI. The mean values did not differ significantly for any of the IgG measurements of the four bacteria. All the antibody readings displayed large standard deviations (SD).

The men with self-reported MI were found to be slightly older, less educated, and more likely to suffer from diabetes compared to non-MI men (Table 2). Other significant differences were observed for systolic blood pressure, total cholesterol, HDL-C, non-fasting glucose, BMI, and triglycerides. Significantly more of the MI-men had visited the general practitioner four times or more last 12 months (40.4 versus 23.3%), but this was not the case for dental visits. The two groups did not differ regarding being on current antihypertensive drugs, 27.3 versus 28.5% whereas the percentage on cholesterol-reducing drugs (as expected) was much higher in the MI-group 63.8 versus 12.8%.

Cox proportional hazards regression analyses were performed to study which variables predicted CVD mortality over the 12 ½-years follow-up (Table 3). In age and age-adjusted univariate analyses, age and the four antigens series. The receiver operating curve (ROC) was used to detect any cut off value of the antibody readings of diagnostic importance. In addition, the area under the curve (AUC) was calculated. A P-value < 0.05 was considered significant. IBM SPSS version 25 was used for the statistical analyses. Kaplan Meier plots Fig. 1 A) and 1B) illustrate cumulative survival according to quartile levels of TF for men with or without a history of MI.

### Table 1

| Bacterial antibodies | Myocardial infarction | No myocardial infarction | p-value |
|----------------------|-----------------------|--------------------------|---------|
|                      | Mean (SD)             | Min-max                  | Quartile values | Mean (SD) | Min-max | Quartile values |
| Porphyromonas gingivalis | 251.6 (603.7) | 12-8710 | 54, 95, 201 | 217.6 (426.6) | 9-5299 | 52, 86, 195 | 0.096 |
| Tannerella forsythia | 94.6 (146.2) | 10-2166 | 33, 53, 102 | 96.8 (121.5) | 9-1204 | 35, 58, 103 | 0.883 |
| Treponema denticola | 74.2 (201.9) | 3-3593 | 26, 44, 74 | 69.3 (93.3) | 1-1240 | 28, 46, 75 | 0.258 |
| Aggregatibacter actinomycetemcomitans | 115.1 (201.9) | 5-3166 | 33, 62, 126 | 101.2 (179.7) | 7-3042 | 32, 54, 104 | 0.130 |

* SD = Standard deviation.
was a significant factor in both groups of men as was non-fasting glucose. Further, in MI, HDL-C predicted mortality inversely (HR = 0.48, 95% CI 0.29–0.80). In non-MI, education (inversely) (HR = 0.92, 95% confidence interval (95% CI) 0.85–0.97), diabetes (HR = 2.66, 95% CI 1.21–5.89), taking antihypertensive medication (inversely) (HR = 0.72, 95% CI 0.56–0.92), and systolic blood pressure (HR = 1.01, 95% CI 1.00–1.02) predicted CVD mortality.

Using multivariable Cox analyses we studied quartile values of antibodies of each bacterium adjusted by age, education, diabetes, daily smoking, and systolic blood pressure (Table 4). We found no significant trend for quartile values on the ordinal scale of 1–4 for any of the antibodies examined separately. Then we studied quartile values using the lowest quartile as reference comparing it to the other quartiles. The results for trend were non-significant for all antibodies for both MI and non-MI except for two of these bacteria, and all three bacteria. The Cox analyses were adjusted for age, education, diabetes, daily smoking, and systolic blood pressure. A 12 ½ years follow-up of the Oslo II-study in 2000.

### Discussion

More men reporting MI at the health screening in 2000 that later died from CVD were found to have low levels of *T. forsythia* antibodies in predictive analyses of 12 ½ years follow-up than non-MI. An 82% increased risk was found when comparing first to the fourth quartile of antibodies for *T. forsythia*. The Kaplan-Meier plot indicate that this risk was maintained throughout the follow-up period. The results showed a high specificity of the first decile to 92.3% (369 tested for the second to the tenth decile among 400 men alive) and a sensitivity of 11.5% (17 tested for the first decile among 147 men who died during follow-up). The ROC curve did not show a distinct threshold value but the AUC was significant for *T. forsythia* (p = 0.010).

### Table 3

Cox-analyses; age and age-adjusted univariate analyses for prediction on total CVD mortality. A 12 ½ years follow-up of the Oslo II-study in 2000.

| Risk factor                  | Myocardial infarction | No myocardial infarction |
|------------------------------|-----------------------|--------------------------|
| Age, year                    | 1.16                  | 1.10–1.23                |
| Education, year              | 1.001                 | 0.96–1.05                |
| Daily smoking, yes           | 1.26                  | 0.81–1.95                |
| Diabetes, yes                | 1.51                  | 0.96–2.38                |
| Total cholesterol, mmol/l    | 1.01                  | 0.86–1.17                |
| HDL-C, mmol/l                | 0.48                  | 0.29–0.80                |
| Systolic blood pressure      | 0.999                 | 0.99–1.01                |
| Body mass index, kg/m²       | 1.03                  | 0.99–1.08                |
| Glucose, non-fasting, mmol/l | 1.09                  | 1.02–1.17                |
| Triglycerides, mmol/l        | 1.10                  | 0.96–1.27                |
| Hs-C-reactive protein, mmol/l| 1.01                  | 0.99–1.03                |
| Alcohol, drink two or more times per week | 1.17 | 0.81–1.69 |
| Hypertensive use, yes        | 0.84                  | 0.70–1.01                |
| Cholesterol reducing drugs, yes | 0.982          | 0.815–1.163              |

### Table 4

Cox-analyses of CVD mortality by observed quartile values of each antibody separately for self-reported myocardial infarction and control persons. Risk by quartile values relative to fourth quartile. The analyses were adjusted for age, education, diabetes, daily smoking, and systolic blood pressure. A 12 ½ years follow-up of the Oslo II-study in 2000.

| Risk factor                  | Myocardial infarction | No myocardial infarction |
|------------------------------|-----------------------|--------------------------|
| TF quartiles                 |                       |                          |
| 1st versus 4th               | 1.82                  | 1.12–2.94                |
| 2nd versus 4th               | 1.42                  | 0.86–2.35                |
| 3rd versus 4th               | 1.27                  | 0.76–2.11                |
| 4th quartile                 | 1.00 (ref)            | 1.00 (ref)               |
| PG quartiles                 |                       |                          |
| 1st versus 4th               | 0.88                  | 0.56–1.39                |
| 2nd versus 4th               | 1.04                  | 0.66–1.65                |
| 3rd versus 4th               | 0.77                  | 0.48–1.23                |
| 4th quartile                 | 1.00 (ref)            | 1.00 (ref)               |
| AA quartiles                 |                       |                          |
| 1st versus 4th               | 0.88                  | 0.56–1.39                |
| 2nd versus 4th               | 0.90                  | 0.57–1.41                |
| 3rd versus 4th               | 0.83                  | 0.53–1.32                |
| 4th quartile                 | 1.00 (ref)            | 1.00 (ref)               |

The first decile of *T. forsythia* versus higher decile values among men reporting MI showed a specificity of 92.3% (369 tested for the second to the tenth decile among 400 men alive) and a sensitivity of 11.5% (17 tested for the first decile among 147 men who died during follow-up). The ROC curve did not show a distinct threshold value but the AUC was significant for *T. forsythia* (p = 0.010).
degree of multiple comparisons of the bacteria were done in order to
explore their risk pattern. Microbiologic and epidemiologic studies
provide plausible immunologic pathways, and it could potentially
support the known notion of a hereditary risk for CVD through the
antibody response pattern. One of the limitations of this study is that it
included elderly men only. This reduces the generalizability of the
results to women. Another limitation is that the MI diagnosis was self-
reported at the health screening. However, MI is a major event in a
person’s life including hospitalization, and we have confidence in this
information.

The association and possible causal relation between “chronic”
periodontitis and CVD have been explored in a number of studies.
Antibodies to periodontal pathogens were associated with different
outcomes of CVD, CHD, stroke or MACE. Pussinen et al investigated
antibodies to AA and PG in a random sample (n = 1163) of men aged
45–74 years in Finland. From this cross-sectional study, they reported
that in persons with a high combined antibody response to PG and AA,
coronary heart disease (CHD) was more common than in persons with a
low response [44]. Aoyama et al examined 364 persons with diagnosed
CVD for tooth extraction status [45]. In comparison of the four groups
of remaining teeth, they found that the level of PG IgG in the group with
10–19 teeth was statistically higher than that in the group with ≥20 teeth.
In their case-control study on stroke, Pussinen et al found that
IgA-serospositive for A. actinomycetemcomitans was higher among the
controls, non-stroke patients, and IgA-serospositive for P. gingivalis
higher among patients with recurrent stroke during 13 years of follow-
up [46]. Beck et al found that systemic antibody response to 17 peri-
odontal bacteria rather than periodontal status was relevant to ather-
othrombotic coronary events (35). The bacteria involved differed be-
 tween smokers and non-smokers. Differences between strains of
bacteria indicate differences in virulence factors as observed by Ya-
mazaki et al for prevalence of serum IgG positivity to 12 periodontal
pathogens [47]. They observed that antibody positivity for
·P.gingivalis FDC381 and P. gingivalis Su63 was higher than the other 11
bacteria and differed between the three groups of 51 CHD patients with
variable degrees of periodontitis, 55 had periodontitis, and 37 were
controls.

Periodontitis has been shown to be related to lower levels of HDL-
cholesterol (HDL-C), a situation that may be reversed after treatment
of periodontitis [17,43]. D’Aiuto et al. have shown in randomized con-
trolled trials that in a study of 6 months duration periodontal therapy
achieved a reduction in CRP, IL-6, total cholesterol, systolic blood
pressure, and the Framingham cardiovascular disease risk score [48].
In a second trial on persons with type 2 diabetes, periodontal treatment
over a period of 12 months significantly reduced HbA1c [49]. Ramirez
et al. studied subgingival “Red complex” bacteria and biomarkers for
CVD. Comparing patients with periodontitis and periodontally healthy
controls they found E-selectin, MPO, and ICAM-1 to be increased
among patients with periodontitis. Other CVD markers studied were
flow-mediated dilatation, CRP, VCAM-1, MMP-9, Adiponectin, and
tPAI-1 [50]. The Danish Nationwide Cohort Study included 17,691
patients who received a hospital diagnosis of periodontitis and com-
pared them to 83,003 controls from the general population [51].
Hansen et al. concluded that periodontitis may be an independent risk
factor for CVD measured by incidence rate ratios, all significant, for
myocardial infarction, ischemic stroke, CVD death, major adverse CVD
events (MACE), and all-cause mortality.

Multiple microbiology studies using several approaches have been
performed in order to understand periodontal disease development -
the metastatic spread of bacteria, the effect, and function of bacterial
virulence factors, and the immune system response [52]. The three
bacteria of the ‘Red complex’ show both competitive and cooperative
interactions [5,53]. They also show genetic variability but according to
Amano et al. changes have not been observed during persistent coloni-
zation. The bacteria of the “Red complex” possess the common fea-
ture of expressing neuraminidases. This enables them to scavenge sialic
acid from host glycoconjugates. The cleaved sialic acid serves as a
nutrient for bacterial growth and aid the bacteria to evade host immune
attack. Another important feature of periodontal pathogens is their
ability to enter into host cells. It has been shown that TD and PG display
syblosis in protein degradation, nutrient utilization, and growth
promotion [54]. The reduced antibody response to TF might be due to
the unusual S-layer of this bacterium where two S-layer glycoproteins
are assembled into a single S-layer [54–56]. The S-layer may be used as
a strategy for this bacterium to evade recognition by the innate immune
system particularly by suppressing Th17 responses [56]. The surface
glycosylation provides a means of manipulation of the cytokine re-
sponse of macrophages and T-cells. The present findings relate myo-
cardial infarction to the metastatic consequences of advanced period-
ontal/dental bacteria and/or bacterial products.

Conclusion

The novel and main finding of this study is the inverse relation for
antibodies towards the periodontopathogen T. forsythia to increased
risk for CVD mortality. T. forsythia is an initiator of advanced “chronic”
periodontal infection, allowing for the progression of periodontitis by
the joint effect of the ‘Red complex’ bacteria on cardiovascular struc-
tures. This throws new light on the relative importance of red complex
members in the development of CVD where P. gingivalis, the keystone
bacterium of periodontitis, has attracted most attention so far. The re-
duced ability to form antibodies to T. forsythia in relation to MI needs to
be studied further to establish whether it represents a general im-
munological deficiency contributing to the pathophysiological me-
chanism resulting in myocardial infarction. The consequence is the
development of a vaccine for persons identified with low levels of an-
tibodies to T. forsythia by a specific ELISA-test particularly in associa-
tion with chronic periodontitis. This finding supports the reports of a
suggested causal link between “chronic” periodontitis to mortality in
persons with myocardial infarction.

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The authors declare that they have no known competing financial
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