Association of high cardiovascular risk and diabetes with calcified carotid artery atheromas depicted on panoramic radiographs

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Objective. To evaluate whether estimates of risk of future cardiovascular events and death and established or unknown diabetes are significantly associated with calcified carotid artery atheromas (CCAAs) on panoramic radiographs (PRs). The main focus was on men and women without previous myocardial infarction (MI).

Methods. The PAROKRANK (Periodontitis and its Relation to Coronary Artery Disease) study included patients with a first MI and matched control subjects. In this substudy, 738 patients (138 women) and 744 control subjects (144 women) with available PRs were assessed for CCAA. Cardiovascular risk estimates were determined according to the Framingham Risk Score (FRS) and Systematic COronary Risk Evaluation (SCORE). Established and previously unknown diabetes was also determined.

Results. CCAA was detected on PRs in 206 control subjects (28%) and 251 patients (34%). FRS was significantly associated with CCAA among control subjects ($P = .04$) and patients ($P = .001$). SCORE was associated with CCAA among control subjects ($P < .01$) but not patients ($P = .07$). Among men, FRS and SCORE were associated with CCAA in both control subjects and patients. Diabetes was not significantly associated with CCAA after adjustments.

Conclusions. Elevated cardiovascular risk scores were associated with CCAA on PRs among control subjects. Diabetes was not independently associated with CCAA, possibly owing to selection bias. (Oral Surg Oral Med Oral Pathol Oral Radiol 2022;133:88−99)

Cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, is the leading cause of death worldwide, resulting in over 15 million deaths in 2016 according to the World Health Organization (WHO).[1] Early detection of signs of CVD and preventive treatment are therefore crucial to reduce disease and death rates. Panoramic examinations are often performed in general dental care, and calcified carotid artery atheromas (CCAAs) are a common incidental finding on panoramic radiographs (PRs) (Figure 1). CCAAs are an indicator of atherosclerotic plaques in the carotid artery, which signify an increased risk of future cardiovascular events.[2-4]

In patients with CCAA on PRs, Doppler ultrasound commonly reveals thickening of the tunica intima and media and some degree of stenosis, indicating an ongoing arteriosclerotic process.[5,6] However, few of these stenoses involve luminal diameter reduction >50%,[6] which is the extent associated with significantly increased stroke risk.[7] Most studies related to this problem have been cross-sectional assessments of the relationship between CCAA and cardiovascular events, providing limited information regarding the use of CCAA to estimate future cardiovascular risk.[8,9]

The prevalence of CCAA seen on PRs in adult populations ranges from 12% to 40%[2,10,11] and increases with age.[11] The prevalence is lower in populations that include participants within a wider age range (9-99 years).[12-14] The presence of CCAA on PRs is associated with MI, and an even stronger association has been shown between CCAA combined with periodontitis and MI.[10,15] Several other studies have also revealed associations between CCAA and different cardiovascular conditions.[16]

The risk of future cardiovascular events and death can be estimated using various risk scores.[17] Two of the most commonly used tools are the Framingham Risk Score (FRS)[18] and Systematic COronary Risk Evaluation (SCORE),[17] which can be used to assess the 10-year risk for cardiovascular events and death. In our lit-

Statement of Clinical Relevance

Calcified carotid artery atheromas on panoramic radiographs indicate an increased estimated risk of cardiovascular disease and death among men ≤75 years of age, suggesting that dentists should refer these patients for further medical attention if previously untreated for cardiovascular disease.

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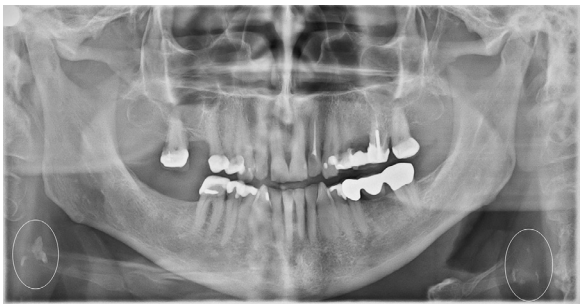

Fig. 1. A panoramic radiograph of teeth and jaws depicting bilateral calcified carotid artery atheromas located at the level of the third and fourth cervical vertebrae as depicted within the white rings.

erature review, we found no studies on the potential association between these risk estimators and CCAA detected on PRs.

CCAA on PRs is more prevalent among patients with type 2 diabetes; however, no investigations have examined associations between CCAA on PRs and previously unknown diabetes or abnormal glucose tolerance.[19-21] If CCAA on PRs is proved to be useful for identifying individuals with CVD, high estimated risk of cardiovascular events, and unknown diabetes, the finding might promote preventive care.

In the present substudy of the PAROKRANK (Periodontitis and its Relation to Coronary Artery Disease) study, we aimed to (1) evaluate whether a higher risk of future cardiovascular events and death estimated with FRS and SCORE was associated with CCAA in PRs by analyzing all participants, with a focus on control subjects without previous MI; (2) investigate whether established or previously unknown diabetes was associated with CCAA among both patients and control subjects; and (3) analyze possible differences between men and women.

MATERIALS AND METHODS

Study population

The present study population was based on the study population of the Swedish multicenter PAROKRANK study, which was conducted at 17 hospitals between 2010 and 2014. The population comprised 1610 individuals with a mean age of 62±8 years, including 805 patients with a first MI (151 women) and 805 matched control subjects with no history of MI (151 women), as described in detail elsewhere.[22] The patients were included on the basis of a diagnosis of acute MI as defined by SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies).[23] Exclusion criteria were previous MI or previous heart valve replacement, age >75 years, residence outside the treating center catchment areas, severe disease that could interfere with participation and dental investigations, and language or cognitive issues. For each patient, a control individual without previous MI or heart valve replacement was selected from the population registry and matched in terms of age (±3 months), sex, and residential region (living in the same area code as the matching case).

Within 6 to 10 weeks after recruitment, all participants underwent a thorough medical and oral examination, in most cases including a PR examination. Participants also completed a questionnaire about medical treatment, previous diseases, smoking habits, and education level. The present analysis excluded participants without a PR (9 control subjects and 8 patients) or those whose PRs were overexposed, had compression defects, or did not depict the area of the carotid artery (52 control subjects and 59 patients), because the presence of CCAA could not be determined. The exclusions resulted in a population of 744 control subjects and 738 patients with a first MI, for a total of 1482 participants. When baseline characteristics between excluded and included participants were compared, there were no significant differences.

Medical examination

All participants were fasting and did not smoke for 12 hours before their examination. Blood samples were obtained for analyses of blood count, plasma lipids (total and high-density lipoprotein [HDL] cholesterol), and plasma glucose. Detailed information about the blood analysis methods is provided by Rydén et al.[22] Height and weight were measured, and body mass index (BMI) was calculated. The physical examination included measurement of heart rate and blood pressure after 5 minutes sitting at rest.

The physician in charge asked patients about their history of previous comorbidities and medications. Established diabetes was categorized as type 1 or 2. Participants without previously known diabetes underwent an oral glucose tolerance test (OGTT) with venous plasma glucose measured in the fasting state and 2 hours after glucose intake (75 g of glucose in 200 mL of water). On the basis of OGTT, participants were divided into three categories according to definitions set by the WHO: normal (<7.8 mmol/L), impaired (7.8-11.0 mmol/L), or abnormal (>11.0 mmol/L) glucose tolerance.[24]

Risk assessment

All participants were assessed for future risk of cardiovascular events using FRS[18,25] and SCORE,[17] which are based on large American and European cohorts, respectively. FRS estimations were performed using the provided algorithm, which is based on age, diabetes, smoking status, treated and untreated systolic blood

pressure, total cholesterol, and HDL cholesterol. SCORE estimations were manually performed using the risk chart for low-risk European countries calibrated for Sweden, which is based on sex, age, total cholesterol, systolic blood pressure, and smoking status.[17]

FRS is used to estimate the 10-year risk for CVD events, including coronary death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure.[25] Participants' risk of future CVD events was classified as low (<5%), slight (5%-9%), moderate (10%-19%), high (20%-39%), or very high (≥40%).

SCORE estimates the 10-year risk of cardiovascular death. Participants' risk of CVD death was classified as low (<1%), moderate (1%-4%), high (5%-9%), or very high (≥10%) (only integer numbers are used in SCORE). Risk assessments were performed using SCORE 2015 for low-risk European countries, which has been validated for a Swedish population in northern Sweden and has been proved to be more accurate than the 2003 SCORE Sweden when used among participants in the 1999 MONICA (monitoring trends and determinants in CVD) study.[26]

In the dichotomized comparison, the risk categories were combined to create low-risk and elevated risk populations. Participants with low and slight risk (<10%) according to FRS were classified as the low-risk reference group and were compared with participants with moderate, high, and very high risk (≥10%). For SCORE, the groups with low and moderate risk of death (<5%) served as the reference and were compared with the groups with a high and very high risk of death (≥5%).

Estimated risks of future cardiovascular events or death were calculated for both control subjects and patients. However, the focus was on the control group without previous MI, which represented a population that could benefit from CVD treatment, since patients who had experienced a previous MI have ongoing preventive CVD treatment. The risk levels as determined with FRS and SCORE were compared in the participants with and without CCAA in the control and patient populations to identify the significance of associations of risk of CVD and death.

The participants were also examined for the association of diabetes and CCAA. They were classified as having established diabetes if they self-reported this diagnosis. Previously unknown diabetes was defined by an abnormal glucose tolerance level on the OGTT, and impaired glucose tolerance was added as a separate category in the association of diabetes with CCAA.

Radiographic assessments

All PRs were individually assessed for CCAA and other calcifications by 2 specialists in oral and maxillofacial radiology, each with more than 10 years of experience in diagnosing CCAA. These observers were blinded to all information about the participants, including group affiliation and sex. In cases of disagreement, the presence of CCAA was discussed until consensus was reached. CCAAs of all sizes and shapes were registered and differentiated from other calcified soft tissues and cartilage such as the triticeous cartilage, superior cornu of the thyroid cartilage, epiglottis, and calcifications in lymphatic nodules.[27-30] Interobserver agreement for the 2 observers in the detection of CCAA was calculated with the κ statistic on the basis of each observer's assessment of all 1482 participants and was considered good ($\kappa = 0.78$).[31] Intraobserver agreement was calculated on the basis of 100 randomly selected duplicate PRs that were inserted in the material without the observers' knowledge. Intraobserver agreement was considered good/very good ($\kappa = 0.80$ and 0.85).[31]

The radiographs, most of which were in a digital format (92%), were evaluated in a dimly lit room. The analog PRs were evaluated with hot-spot illumination and with Mattson binocular magnification. Digital PRs were viewed on high-resolution monitors using OsiriX MD (Pixmeo, Geneva, Switzerland) or Preview (Apple Inc., Cupertino, CA) software. The observers adjusted the contrast and light levels in the digital images to optimize conditions for CCAA detection.

Statistics

Control subjects and patients were separately analyzed using the R software environment for statistical computing (R Core Team, 2019) and IBM SPSS Statistics 24 (IBM, Armonk, NY) statistical software. We analyzed associations of CVD risk estimations (FRS and SCORE) and diabetes with CCAA using logistic regression and presented the results as both crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Adjustment of the associations with CVD risk only included education level because all other possible confounders were considered in the risk scores. Associations with diabetes were adjusted for age, sex, BMI, and education level. A P value $\leq .05$ was considered to indicate a significant difference.

The risk estimations were assumed to be linear because we observed no significant gain from not assuming linearity. ORs were evaluated according to different classifications with the data divided into all different risk categories, using the low-risk group as the reference. ORs were also evaluated for dichotomized groupings, with the moderate to very high−risk group compared with the reference low to slight risk−group for FRS and the high to very high−risk group compared with the low to moderate risk−group for SCORE, followed by OR calculation between participants with and without CCAA.

In the demographic and background characteristics, as well as the medical examination results, the difference

between groups was evaluated with the Student *t* test for age (mean), BMI, cholesterol, triglycerides, fasting glucose (mean), and systolic and diastolic blood pressure. For all other variables, logistical regression was used.

Ethical considerations

The PAROKRANK study was approved by the Regional Ethics Committee in Stockholm (Dnr:2008/152-31/2). All patients provided written informed consent before inclusion, and the study was conducted according to the principles outlined in the Declaration of Helsinki.

RESULTS

CCAA was detected on PRs of 206 (67 bilateral) of the 744 control subjects (28%), and in 251 (101 bilateral) of the 738 patients (34%), representing a significantly greater prevalence in the patients ($P = .008$).[10] Table I presents the pertinent demographic and background characteristics and medical examination results according to the presence of CCAA for each study group. Among control subjects, those with CCAA were older and had higher triglyceride and fasting glucose levels, higher BMI, and greater frequency of hypertension than the control subjects without CCAA. Among patients, those with CCAA were older and had higher cholesterol and fasting glucose levels, higher systolic blood pressure values, and a greater frequency of hypertension, but were not as frequently current and previous smokers, compared with patients without CCAA.

Estimated cardiovascular risk

Associations between FRS and CCAA. Assessment of control subjects in the separate risk categories according to FRS, establishing the low-risk group (<5%) as the

Table I. Pertinent characteristics of control subjects and patients with recent first myocardial infarction, grouped according to presence or absence of calcified carotid artery atheromas detected on panoramic radiographs

Control subjects		*CCAA (n = 206)*		*No CCAA (n = 538)*	*P value*
Women, n (%)	46	(22)	98	(18)	.24*
Age, y, median (IQR)	65	(60-69)	63	(57-67)	< **.01***,‡
Age, y, mean (min-max)	64	(33-75)	62	(28-75)	< **.01**†,‡
University educated, n (%)	76	(37)	212	(40)	.59*
Current or previous smoker, n (%)	166	(80)	423	(79)	.47*
Cholesterol, mmol/L, mean (SD)	5.7	(1.2)	5.5	(1.1)	.08†
Triglycerides, mmol/L, mean (SD)	1.6	(1.3)	1.4	(1.2)	**.05**†,‡
Fasting glucose, mmol/L, mean (SD)	5.8	(1.6)	5.5	(1.1)	**.04**†,‡
Fasting glucose, mmol/L, median (IQR)	5.6	(5.0-6.2)	5.4	(4.9-5.9)	.06*
BMI, kg/m^2, mean (min-max)	27.4	(19-52)	26.6	(18-42)	**.03**†,‡
Systolic blood pressure, mmHg, mean (SD)	138.7	(17.2)	136.8	(17.4)	.18†
Diastolic blood pressure, mmHg, mean (SD)	83.3	(9.9)	83.6	(10.3)	.75†
Hypertension, n (%)	92	(44.2%)	160	(29.9%)	< **.01***,‡
Patients		*CCAA (n = 251)*		*No CCAA (n = 487)*	P *value*
Women, n (%)	53	(21)	85	(18)	.27*
Age, y, median (IQR)	65	(61-69)	62	(56-67)	< **.01***,‡
Age, y, mean (min-max)	64	(33-74)	61	(28-74)	< **.01**†,‡
University education, n (%)	83	(33)	170	(35)	.68*
Current or previous smoker, n (%)	208	(82)	419	(86)	**.01***,‡
Cholesterol, mmol/L, mean (SD)	4.0	(0.8)	3.8	(0.9)	**.04**†,‡
Triglycerides, mmol/L, mean (SD)	1.2	(0.6)	1.4	(1.1)	.07†
Fasting glucose, mmol/L, mean (SD)	6.2	(1.7)	5.9	(1.3)	**.02**†,‡
Fasting glucose, mmol/L, median (IQR)	5.9	(5.4-6.5)	5.7	(5.3-6.2)	< **.01***,‡
BMI, kg/m^2, mean (min-max)	27.2	(17-43)	27.1	(18-44)	.76†
Systolic blood pressure, mmHg, mean (SD)	132.5	(18.4)	127.9	(15.9)	< **.01**†,‡
Diastolic blood pressure, mmHg, mean (SD)	77.3	(10.7)	76.2	(9.6)	.16†
Hypertension, n (%)	104	(41.6%)	163	(33.6%)	**.03***,‡

BMI, body mass index; *CCAA*, calcified carotid artery atheroma; *IQR*, interquartile range; *MI*, myocardial infarction; *min-max*, minimum and maximum values; *SD*, standard deviation.
*Logistic regression.
†Student *t* test.
‡*P* value ≤ .05.

reference, revealed that very high risk (≥40%) of a cardiovascular event or death was associated with CCAA (OR, 4.22; 95% CI, 1.62-12.52; $P = .005$). In the dichotomous group comparisons, the merged category moderate and very high risk (≥10%) of cardiovascular event or death according to FRS was significantly associated with CCAA (OR, 1.64; 95% CI, 1.03-2.64; $P = .04$) when using the merged low and slight−risk category (<10%) as the reference (Table II).

In sex-stratified analyses among male control subjects, increased estimated risk of cardiovascular event or death based on FRS was associated with CCAA for the very high−risk group compared with the reference category (OR, 6.48; 95% CI, 1.65-43.30; $P = .02$). Comparisons in the dichotomous groups revealed a significant association with CCAA for the moderate and very high−risk group (OR, 2.76; 95% CI, 1.34-5.70; $P = .006$). Corresponding analysis among women showed no significant associations for individual risk comparisons ($P \geq .13$) or in the dichotomized groups ($P = .70$), as listed in Table II.

Among patients with recent MI, the slight- (5%-9%), moderate- (10%-19%), high- (20%-39%), and very high (≥40%)−risk groups as classified by FRS were significantly associated with CCAA when using low risk as the reference ($P \leq .04$). Analysis using the dichotomized FRS for risk of cardiovascular events and death, with low and slight risk as the reference, revealed that moderate and very high risk was associated with CCAA (OR, 1.89; 95% CI, 1.31-2.73; $P = .001$), as listed in Table II.

In the sex-stratified analysis of the patients with recent MI, we found that the moderate-, high-, and very high−risk FRS categories among men were significantly associated with CCAA ($P \leq .05$), as were slight, moderate, and high risk among women ($P \leq .04$). In the dichotomized data, male patients exhibited an association between moderate and very high risk and CCAA (OR, 2.47; 95% CI, 1.55-3.92; $P < .001$). However, the relationship between the moderate and very high−risk category with CCAA in women compared with the low and slight−risk reference group was not significant ($P = .40$), as listed in Table II. All of the presented associations were based on results after adjustments for education level. Bilateral CCAA was not significantly more common in any risk category compared with participants with unilateral CCAA, among control subjects or patients ($P > .05$).

Associations between SCORE and CCAA

Among control subjects, the separate SCORE categories of risk of death (moderate, high, and very high) showed no significant association with CCAA compared with the low-risk reference category ($P \geq .08$). However, the dichotomized category of high and very high risk (≥5%) according to SCORE was significantly associated with CCAA (OR, 1.58; 95% CI, 1.12-2.23; $P < .01$), using low to moderate risk (<5%) as the reference, as revealed in Table II.

In the sex-stratified analysis among male control subjects, none of the separate risk categories were significantly related to CCAA ($P \geq .07$), but the dichotomized high and very high−risk group was associated with CCAA (OR, 1.57; 95% CI, 1.08-2.28; $P = .02$). Among female control subjects, no significant associations were found between SCORE and CCAA for the separate risk groups ($P \geq .50$) or the dichotomized groups ($P = .78$). All data are presented in Table II.

Among patients with recent MI, when using low risk as the reference, an association was discovered between the separate categories of high and very high risk of death and the presence of CCAA ($P \leq .04$). In the dichotomized analysis, however, high and very high risk of death was not significantly associated with CCAA (OR, 1.39; 95% CI, 0.98-1.99; $P = .07$), using low and moderate risk as the reference (Table II).

In the sex-stratified analysis of patients, the categories of high and very high risk were associated significantly with CCAA ($P \leq .03$) in men, but no significant associations were discovered in women for any risk category ($P \geq .40$). With dichotomized grouping, increased risk of cardiovascular death (the high and very high risk category) was associated with CCAA among both men and women after adjustments ($P = .05$), as listed in Table II.

All of these analyses were adjusted for education level. Participants with bilateral CCAA were not significantly more common in any risk category compared with participants with unilateral CCAA among control subjects or patients ($P > .05$).

Diabetes

Control subjects. Established or previously unknown diabetes was present in 37 (18.0%) of the 206 control subjects with CCAA and in 63 (11.7%) of the 538 control subjects without CCAA, which represented a significantly greater prevalence of diabetes in the control subjects with CCAA in the univariate analysis ($P = .03$). Previously unknown diabetes (abnormal glucose tolerance; >11.0 mmol/L measured in the OGTT) was found in 14 (6.8%) of the 206 control subjects with CCAA and 27 (5.0%) of the 538 control subjects without CCAA. When we included impaired glucose tolerance (7.8-11.0 mmol/L), these numbers increased to 61 (29.6%) of the control subjects with CCAA and 127 (23.6%) of control subjects without CCAA.

In the unadjusted analysis, control subjects with established diabetes were more likely to have CCAA (OR, 1.76; 95% CI, 1.00-3.03; $P = .04$); however, this association did not remain significant after adjustments for age, BMI, and education level (OR, 1.40; 95% CI,

Table II. Associations between cardiovascular risk and calcified carotid artery atheromas on panoramic radiographs, according to Framingham Risk Score and Systematic COronary Risk Evaluation among control subjects and patients with recent first myocardial infarction

		OR (95% confidence interval), P value (n = control subjects/patients)											
		All (n = 744/738)				*Men (n = 600/600)*				*Women (n = 144/138)*			
	Category (with CCAA/all) [with CCAA/women]	*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**	
FRS control subjects (n = 744)	Low (12/59) [6/26]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Slight (14/70) [10/28]	1.42 (0.54-4.21)	.5	1.42 (0.54-4.21)	.5	1.21 (0.26-8.73)	.82	1.21 (0.26-8.66)	.83	1.96 (0.55-8.03)	.31	1.96 (0.56-8.8.05)	.31
	Moderate (63/253) [20/67]	1.71 (0.72-4.72)	.25	1.68 (0.71-4.64)	.27	2.40 (0.65-15.59)	.25	2.40 (0.65-15.54)	.26	1.59 (0.50-6.13)	.45	1.52 (0.48-5.85)	.51
	High (89/300) [10/23]	2.18 (0.93-5.95)	.09	2.19 (0.94-5.98)	.09	3.19 (0.88-20.48)	.13	3.19 (0.88-20.48)	.13	2.88 (0.76-12-61)	.13	2.89 (0.76-12.63)	.13
	Very high (28/62) [0/0]	4.25 (1.63-12.62)	**.005**†	4.22 (1.62-12.52)	**.005**†	6.58 (1.68-43.94)	**.02**†	6.48 (1.65-43.30)	**.02**†	NA		NA	
	Low-slight (26/129) [16/54]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Moderate-very high (180/615) [30/90]	1.66 (1.03-2.65)	**.04**†	1.64 (1.03-2.64)	**.04**†	2.76 (1.33-5.68)	**.006**†	2.76 (1.34-5.70)	**.006**†	1.18 (0.57-2.46)	.65	0.70 (0.55-2.41)	.70
FRS patients (n = 738)	Low (16/85) [7/29]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Slight (38/140) [18/42]	2.79 (1.11-8.52)	**.04**†	2.79 (1.11-8.52)	**.04**†	1.78 (0.55-7.98)	.38	1.77 (0.55-7.95)	.39	6.46 (1.59-43.92)	**.02**†	6.59 (1.62-44.89)	**.02**†
	Moderate (101/292) [19/49]	3.80 (1.57-11.34)	**.01**†	3.80 (1.58-11.33)	**.01**†	3.39 (1.12-14.70)	**.05**†	3.39 (1.12-14.67)	**.05**†	5.06 (1.25-34.35)	**.04**†	5.30 (1.28-36.34)	**.04**†
	High (78/186) [8/16]	5.20 (2.12-15.66)	< **.001**†	5.19 (2.11-15.63)	< **.001**†	4.66 (1.52-20.34)	**.02**†	4.61 (1.51-20.13)	**.02**†	8.00 (1.57-62.00)	**.02**†	8.92 (1.72-70.34)	**.02**†
	Very high (18/35) [1/2]	7.62 (2.57-26.34)	< **.001**†	7.59 (2.56-26.26)	< **.001**†	7.08 (1.95-34.30)	**.005**†	6.91 (1.90-33.52)	**.01**†	8.00 (0.25-273.15)	.19	6.20 (0.19-216.44)	.24
	Low-slight (54/225) [25/71]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Moderate-very high (197/513) [28/67]	1.90 (1.31-2.73)	< **.001**†	1.89 (1.31-2.73)	**.001**†	2.48 (1.56-3.94)	< **.001**†	2.47 (1.55-3.92)	< **.001**†	1.31 (0.65-2.64)	.45	1.36 (0.66-2.78)	.40

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Table II. Continued

		OR (95% confidence interval), P value (n = control subjects/patients)											
		All (n = 744/738)				*Men (n = 600/600)*				*Women (n = 144/138)*			
	Category (with CCAA/all) [with CCAA/women]	*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**	
SCORE control subjects (n = 744)	Low (5/30) [3/11]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Moderate (128/481) [38/121]	1.99 (0.74-6.91)	.21	2.01 (0.75-6.99)	.21	4.66 (0.92-85.16)	.13	4.78 (0.94-87.19)	.13	1.22 (0.33-5.80)	.77	1.19 (0.32-5.67)	.80
	High (65/201) [5/12]	2.62 (0.95-9.26)	.09	2.69 (0.98-9.48)	.08	6.51 (1.26-119.35)	.07	6.69 (1.30-122.58)	.07	1.90 (0.33-12.23)	.47	1.91 (0.34-12.27)	.50
	Very high (8/32) [0/0]	1.83 (0.50-7.66)	.37	1.82 (0.50-7.63)	.38	4.66 (0.74-92.28)	.17	4.64 (0.74-90.76)	.17	NA		NA	
	Low-moderate (133/511) [41/132]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	High-very high (73/233) [5/12]	1.55 (1.11-2.19)	**.01**†	1.58 (1.12-2.23)	< **.01**†	1.56 (1.07-2.27)	**.02**†	1.57 (1.08-2.28)	**.02**†	1.09 (0.45-2.63)	.86	1.13 (0.46-2.77)	.78
SCORE patients (n = 738)	Low (11/42) [5/12]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	Moderate (185/582) [43/117]	1.46 (0.64-3.76)	.38	1.46 (0.64-3.75)	.39	1.86 (0.67-6.58)	.26	1.88 (0.68-6.63)	.26	0.97 (0.22-4.90)	.90	1.07 (0.25-5.57)	.90
	High (48/103) [5/9]	2.74 (1.12-7.45)	**.03**†	2.73 (1.12-7.42)	**.04**†	3.58 (1.21-13.27)	**.03**†	3.57 (1.21-13.15)	**.03**†	2.08 (0.30-16.14)	.40	2.44 (0.35-19.54)	.40
	Very high (7/11) [0/0]	5.50 (1.28-26.90)	**.03**†	5.49 (1.29-26.85)	**.03**†	7.44 (1.53-43.30)	**.02**†	7.49 (1.55-43.63)	**.02**†	NA		NA	
	Low-moderate (196/624) [48/129]	*Ref*		*Ref*		*Ref*		*Ref*		*Ref*		*Ref*	
	High-very high (55/114) [5/9]	1.39 (0.98-1.99)	.07	1.39 (0.98-1.99)	.07	1.49 (1.01-2.21)	**.05**†	1.49 (1.00-2.19)	**.05**†	2.74 (0.98-7.63)	.06	2.81 (1.01-7.88)	**.05**†

Odds ratios (ORs) were determined using two methods: using low risk as a reference (*Ref*) for Framingham Risk Score (FRS) and Systematic Coronary Risk Evaluation (SCORE) compared with all categories; and dichotomized, with references (*Ref*) representing low and slight risk for FRS and low and moderate risk for SCORE. ORs were calculated using logistic regression and are presented with a 95% confidence interval. Adjustments were made for education level. Other possible risk factors were included in the risk scores.

CCAA, calcified carotid artery atheroma; *NA*, not applicable; *Ref*, reference.

*Adjusted for education level.

†*P* value ≤ .05.

0.78-2.47; P = .24). In the unadjusted sex-stratified analysis of control subjects, there was a significant difference between men with both established and unknown diabetes with and without CCAA (OR, 1.72; 95% CI, 1.06-2.77; P = .03). However, this difference disappeared after adjustments (OR, 1.28; 95% CI, 0.77-2.11; P = .33). No significant associations were revealed among women for any diabetes classification and CCAA ($P \geq .2$), as listed in Table III.

Patients. Established or previously unknown diabetes was found in 56 (22.3%) of the 251 patients with CCAA and 85 (17.5%) of the 487 patients without CCAA, but the difference was not significant (P = .1). Of these patients, previously unknown diabetes was detected in 26 (10.4%) of the patients with CCAA and 40 (8.3%) of the patients without CCAA. Established diabetes, previously unknown diabetes, or impaired glucose tolerance was found in 122 (44.6%) of the patients with CCAA compared with 176 (36.1%) of the patients without CCAA.

In the univariate model, patients with established diabetes, previously unknown diabetes, or impaired glucose tolerance exhibited an increased OR for CCAA (OR, 1.42; 95% CI, 1.04-1.94; P = .03); however, this difference disappeared after adjustments (OR, 1.19; 95% CI, 0.85-1.65; P = .31). In analysis of men, the univariable model revealed similar unadjusted results (OR, 1.51; 95% CI, 1.07-2.15; P = .02), with loss of significance when data were adjusted (OR, 1.22; 95% CI, 0.85-1.77; P = .28). Among women, there were no significant associations between diabetes status and CCAA for any of the diabetes classifications in either the unadjusted ($P \geq$ .51) or adjusted ($P \geq .4$) results.

DISCUSSION

The main result of this investigation was that a higher cardiovascular risk profile was significantly associated with incidental findings of CCAA based on PRs among control subjects, indicating that these individuals carried an increased risk of cardiovascular events or death compared with control subjects without CCAA. A similar association was observed among patients with a recent first MI. Both the 10-year risk for cardiovascular events or death estimated with FRS and 10-year risk of cardiovascular death estimated by SCORE were significantly associated with CCAA, particularly among men (Table II). Thus, findings of CCAA based on PR of the jaws may be considered a risk marker for CVD.

In our cohort, this association was more pronounced among men than among women. In male control subjects and patients, as assessed with both the FRS and SCORE categories, the presence of CCAA was significantly more likely in the more severe risk categories. Among the women control subjects, neither FRS nor SCORE risk factors were associated with CCAA. For the women with a history of MI, SCORE but not FRS was associated with CCAA (Table II). However, this does not exclude the possibility that CCAA could also be a useful risk marker in women. The finding that increased cardiovascular risk was mainly associated with CCAA among men could be related to the age of the participants, who were all 75 years old or younger at the time of inclusion in the study, with a mean age of 62 years. It is well known that women have a later onset of CVD than men, and therefore fewer were included in this consecutive cohort. Similar sex differences have also been shown in previous reports of cohorts with a mean age younger than 75 years.[3,10] It is also notable that there were fewer women than men in our cohort, with women comprising 19% of the study population, and only 99 women had CCAA. Thus, when subdivided into different risk categories, the groups of women were small, such that significant associations might be missed.

High scores on FRS and SCORE indicate an increased prevalence of underlying risk factors in any population, which is associated with a greater risk of future cardiovascular events and death. The higher estimated risk among control subjects with CCAA calculated with FRS and SCORE can partly be explained by a higher mean age and a higher prevalence of hypertension. For FRS, diabetes may also contribute to the higher risk estimate. Furthermore, among patients, higher age, cholesterol, fasting glucose levels, and blood pressure may have contributed to the higher risk estimates (Table I). The "high risk" category for SCORE is set at 5% in all European countries. In Sweden, however, the levels of underlying risk factors must be higher to be classified as a 5% risk compared with other low-risk countries and all high-risk countries.[17] This can be explained by the low mortality rate within 30 days after MI in Sweden (7.6%) compared with rates in other countries, such as 10.5% in the United Kingdom.[32] Therefore, it is important to use risk scores that have been validated for the country from which the cohort originates; in this case, Sweden. Because SCORE only predicts fatality, it was important to strengthen our observations through the use of FRS, which includes a variety of cardiovascular events. However, both tools have limitations regarding risk estimation for participants with diabetes, in whom the risk may be underestimated. The results of our present investigation, combined with previous evidence of increased risk for MI,[4,10] stroke,[3,16] and other CVD in long-term follow-up,[3] indicate that patients without previously diagnosed CVD but with incidental findings of CCAA based on PR should be advised to seek (or be referred for) further evaluation of cardiovascular risk factors by a physician.[33,34]

As in previous studies, univariate models showed associations between diabetes and CCAA that disappeared in the multivariate model.[5,21,35,36] Thus, established or

Table III. Associations between diabetes mellitus and calcified carotid artery atheromas detected on panoramic radiographs among control subjects and patients with recent first myocardial infarction

		OR (95% confidence interval), P value (n = control subjects/patients)											
		All (n = 744/738)				*Men (n = 600/600)*				*Women (n = 144/138)*			
	Category (with CCAA/all with DM) [with CCAA/women with DM]	*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**		*Unadjusted*		*Adjusted**	
Control subjects (n = 744)	Established diabetes (23/59) [2/5]	1.76 (1.00-3.03)	**.04**†	1.40 (0.78-2.47)	.24	1.71 (0.94-3.05)	.07	1.20 (0.64-2.20)	.56	3.35 (0.54-26.12)	.2	2.87 (0.44-23.14)	.3
	Previously unknown diabetes (14/41) [3/7]	1.11 (0.73-1.68)	.6	0.96 (0.62-1.46)	.86	1.15 (0.72-1.81)	.6	0.96 (0.59-1.53)	.86	0.99 (0.35-2.56)	1.0	1.01 (0.35-2.65)	1.0
	Both established and unknown diabetes (37/100) [5/12]	1.66 (1.06-2.57)	**.03**†	1.36 (0.85-2.15)	.19	1.72 (1.06-2.77)	**.03**†	1.28 (0.77-2.11)	.33	1.59 (0.45-5.26)	.5	1.43 (0.39-4.89)	.6
	Impaired glucose tolerance, and established and unknown diabetes (93/188) [10/17]	1.36 (0.96-1.95)	.09	1.12 (0.76-1.63)	.56	1.40 (0.95-2.01)	.09	1.05 (0.69-1.60)	.81	1.32 (0.55-3.17)	.53	1.05 (0.69-1.59)	.81
Patients (n = 738)	Established diabetes (30/75) [2/9]	1.33 (0.81-2.17)	.2	1.10 (0.65-1.83)	.7	1.28 (0.71-2.26)	.4	1.00 (0.54-1.80)	1.0	1.38 (0.52-3.59)	.51	1.55 (0.55-4.30)	.4
	Previously unknown diabetes (26/66) [3/10]	1.31 (0.94-1.82)	.1	1.15 (0.81-1.61)	.4	1.44 (0.99-2.09)	.052	1.25 (0.84-1.83)	.3	0.86 (0.41-1.80)	.70	0.81 (0.37-1.74)	.6
	Both established and unknown diabetes (56/141) [12/30]	1.34 (0.92-1.95)	.1	1.13 (0.75-1.68)	.6	1.41 (0.92-2.16)	.1	1.12 (0.71-1.75)	.6	1.07 (0.46-2.44)	.87	1.11 (0.45-2.67)	.8
	Impaired glucose tolerance, and established and unknown diabetes (112/228) [25/64]	1.42 (1.04-1.94)	**.03**†	1.19 (0.85-1.65)	.31	1.51 (1.07-2.15)	**.02**†	1.22 (0.85-1.77)	.28	1.05 (0.53-2.09)	.88	1.05 (0.51-2.19)	.89

Established diabetes includes patients with self-reported diabetes. Previously unknown diabetes (abnormal glucose tolerance) and impaired glucose intolerance were determined using an oral glucose tolerance test. Odds ratios (ORs) are calculated using logistical regression.

CCAA, calcified carotid artery atheroma; *DM*, diabetes mellitus.

*Adjusted for age, sex, body mass index, and education level.

†*P* value ≤ .05.

previously undetected diabetes was not independently associated with CCAA. Furthermore, we found no independent association between established diabetes, previously unknown diabetes, or impaired glucose tolerance and CCAA among either patients with a previous MI or control subjects (Table III). This may be related to the small number of participants with diabetes, particularly the control subjects with previously unknown diabetes. Furthermore, the control subjects with CCAA had a higher mean BMI (Table I). Another reason may be a selection bias related to the exclusion criteria, which may have led to an overrepresentation of individuals with relatively uncomplicated diabetes.

We did not find a significantly higher prevalence of bilateral CCAA compared with unilateral CCAA in any category of the FRS or SCORE risk estimates. An earlier study reported associations between a higher risk of CVD events in patients with bilateral CCAA compared with unilateral CCAA that we could not confirm.[34] However, this could be explained by the small number of participants with bilateral CCAA in each risk category.

Overall, our findings indicated an association between elevated risk of CVD and CCAA. Therefore, CCAA may be a useful tool for identifying individuals, especially male individuals, without cardiovascular symptoms who are at increased risk of CVD and thus in need of further examination by a physician to reveal other potential risk factors, such as hyperlipidemia, hypertension, obesity, and diabetes. These findings support previous results.[2,3,10,37] It would be interesting to perform a long-term follow-up investigation to determine the extent to which these predictions are correct (i.e., study the prevalence of future CVD events) and thus offer further insight into the diagnostic value of CCAA. There is also a need to confirm the present results with long-term studies in larger cohorts and in a controlled study to evaluate if intervention can decrease the risk of CVD among patients with detectable CCAA on PRs.

Because most PRs are performed by general dental practitioners, these clinicians must be able to evaluate PRs for the presence of CCAA. The ability to correctly identify CCAAs and differentiate them from other calcifications in the area often requires at least a short training program.[38] In the future, novel techniques such as artificial intelligence might improve such diagnostic measures, supporting dental practitioners.

Strengths and weaknesses

The main strengths of this study are the large population investigated with PRs and the use of validated instruments for CVD risk estimation. The geographic coverage is also a strength that contributes to the generalizability of our findings. Regarding diabetes, this study is unique owing to the assessment of the association between CCAA on PR and previously unknown diabetes and the inclusion of other covarying factors in the models. The main limitations are the small number of female participants and the small proportion of participants with previously unknown diabetes, which resulted in limited numbers of participants in some categories, imposing a risk of a type I statistical error. Therefore, we performed a complementary analysis with dichotomized assessments of FRS and SCORE and merging of groups with diabetes. Overall risk estimations, such as FRS and SCORE, have limitations on an individual level but are useful and give a fair estimation of the risk for future cardiovascular events on a population level.[26]

CONCLUSIONS

CCAA seen on PRs was associated with an increased estimated risk of future cardiovascular events and death according to FRS and SCORE among control subjects without previous MI, in particular among male control subjects. In addition, there was a similar relationship in patients with a recent first MI. These findings suggest that a finding of CCAA on PR should encourage dentists to refer such patients for further medical examination of cardiovascular risk factors. Diabetes was not independently associated with CCAA in the present cohort, which may be due to a limited sample size of individuals with uncomplicated diabetes.

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