

Carotid calcifications in panoramic radiographs in relation to carotid stenosis

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Front page: Panoramic radiograph illustrating striking bilateral carotid artery calcifications. Carotid ultrasound revealed a right sided carotid stenosis of 55% and a left sided nonstenotic atherosclerotic plaque.

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To my family

“Man erblickt nur, was man schon weiß und versteht”

Johann Wolfgang von Goethe

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Abstract

Objectives Calcifications in carotid atheromas can be detected in a panoramic radiograph (PR) of the jaws. A carotid artery calcification (CAC) can indicate presence of significant ($\geq 50\%$) carotid stenosis (SCS). The aim of this thesis was to (1) determine the prevalence of SCS and burden of atherosclerotic disease among patients revealing CACs in PRs, (2) determine the prevalence of CACs in PRs among patients with SCS, (3) analyze whether the amount of calcium and/or (4) the radiographic appearance of the CACs, can improve the positive predictive value (PPV) for SCS detection among patients with CACs in PRs.

Material and methods The thesis is based on four cross-sectional studies. Two patient groups were prospectively and consecutively studied. Group A represented a general adult patient population in dentistry examined with PR presenting incidental findings of CACs. These patients were examined with carotid ultrasound for presence or absence of SCS and their medical background regarding atherosclerotic related diseases and risk factors was reviewed. An age and gender matched reference group was included for comparisons. Group B comprised patients with ultrasound verified SCS, examined with PR prior to carotid endarterectomy. The PRs were analysed regarding presence of CACs. The extirpated plaques were collected and examined with cone-beam computed tomography (CBCT) to determine the amount of calcium. The radiographic appearance of CACs in PRs from Group A and B were evaluated for possible association with presence of SCS.

Results In Group A, 8/117 (7%) of patients with CAC in PRs revealed SCS in the ultrasound examination, all were found in men (8/64 (12%)). Patients with CACs in PRs revealed a higher burden of atherosclerotic disease compared to participants in the reference group ($p < 0.001$). In Group B, where all patients had SCS, 84% revealed CACs in PRs and 99% of the extirpated plaques revealed calcification. CACs with volumes varying between 1 and 509 mm³ were detected in the PRs. The variation in volume did not correlate to degree of carotid stenosis. The radiographic appearance that was most frequently seen in neck sides with SCS (65%) was also frequently found in neck sides without SCS (47%) and therefore the PPV did not improve compared to the PPV solely based on presence of CACs.

Conclusions CACs in PRs are more associated with SCS in men than in a general population and patients with CACs in PRs have a higher burden of atherosclerotic disease. The majority of patients with SCS show CACs in PRs and the majority of extirpated carotid plaques reveal calcification. The

volume of CAC and specified radiographic appearance does not increase the PPV for SCS in patients with CACs in PRs. In conclusion patients with CACs in PRs, and without previous record of cardiovascular disease, should be advised to seek medical attention for screening of cardiovascular risk factors.

Enkel sammanfattning på svenska

Bakgrund Inom ramen för specialist- och allmäntandvård utförs panoramaröntgen-undersökningar dagligen på såväl barn som vuxna. En panoramaröntgenbild (PB) är en översiktssbild som är specifikt anpassad till att återge området för tänder och käkar. Utöver det, avbildas även delar av halsen och som bifynd ibland förkalkningar belägna i området för halspulsådern (karotiskärlet). Dessa förkalkningar kallas för karotisförkalkningar och är ett tecken på åderförkalkning.

Åderförkalkning består i huvudsak av en fettrik plackansamling i kärlväggen. Placket kan med tiden förkalkas till varierande grad. Det är dessa förkalkningar vi kan se i PB. När en åderförkalkning ökar i volym kan den utgöra en förträngning i kärlet. Då förträngningen av kärldiametern är $\geq 50\%$ benämns åderförkalkningar belägna i karotiskärlet för ”signifikanta karotisstenosor” (SKS). Graden av förträngning bedöms som regel med ultraljudsundersökning av halskärlen. Bitar av SKS kan lossna varvid det bildas små blodproppar. Eftersom halspulsådern försörjer främre hjärnhalvan med blod så kan dessa bitar täppa till ett av hjärnans blodförsörjande kärl och leda till stroke (slaganfall). För att minska risken att drabbas av stroke kan man ibland operera bort SKS (karotisplacket).

Syfte Syftet med denna avhandling var att ta reda på (1) hur många av de patienter som blir undersökta med PB inom tandvården som uppvisar karotisförkalkningar, hur stor andel som har SKS samt utreda om patienter med förkalkningar i PB i större utsträckning är drabbade av hjärt-kärlsjukdomar/risk faktorer, (2) hur ofta utopererade karotisplock innehåller kalk och hur ofta patienter med känd SKS uppvisar karotisförkalkningar i PB, (3) huruvida förkalkningsmängden i utopererade karotisplock är korrelerad till förträngningsgrad, och (4) huruvida det finns något specifikt radiografiskt utseende på karotisförkalkningar i PB som kan användas för att identifiera en större andel patienter med SKS bland patienter som uppvisar karotisförkalkningar i PB, det vill säga minska risken för att skicka patienter utan SKS på ultraljudsundersökning.

Material och metoder Materialet bestod av två huvudgrupper av patienter. Grupp A bestod av patienter undersökta inom tandvården med PB som uppvisat karotisförkalkningar. Alla dessa patienter undersöktes med ultraljud för att bedöma förekomst av SKS. Den medicinska journalen granskades avseende tidigare förekomst av åderförkalkningsrelaterade sjukdomar och risk faktorer. En köns- och åldersmatchad kontrollgrupp utan karotisförkalkningar i PB analyserades på motsvarande sätt för jämförelse.

Grupp B bestod av patienter med känd SKS som före operativt avlägsnande av karotisplack undersöktes med PB. PB granskades avseende förekomst av karotisförkalkning och utopererade karotisplack avseende kalkinnehåll. Förkalkningsmängden i de utopererade karotisplacken korrelerades dels till möjlighet att identifiera karotisförkalkning i PB samt till förträngningsgraden i kärlen. Karotisförkalkningarnas utseende delades in i grupper för att utvärdera om vissa utseenden i större utsträckning kunde associeras till förekomst av SKS.

Resultat I Grupp A uppvisade 8/117 (7%) patienter SKS, alla var män, 8/64 (12%). Patienter med karotisförkalkningar i PB hade oftare åderförkalkningsrelaterade sjukdomar och risk faktorer ($p < 0,001$). I Grupp B hade 84% av patienterna med SKS karotisförkalkning i PB. Bland de utopererade karotisplacken innehöll 99% förkalkningar och förkalkningsvolymen varierade från 1-509 mm³. Möjligheten att upptäcka karotisförkalkning i PB var oberoende av om förkalkningsvolymen var stor eller liten. Förkalkningsvolymen var heller inte korrelerad till hur stor förträngning av kärlet en SKS ($\geq 50\%$) orsakat. Ett radiografiskt utseende på karotisförkalkningar i PB noterades i 65% av de halssidor som hade en SKS. Detta specifika radiografiska utseende återfanns dock även i 47% av halssidor utan SKS. Andelen falskt positiva patienter var således fortsatt hög.

Slutsats Vi fann att 12% män med karotisförkalkningar i PB, undersökta i en generell population inom tandvården, uppvisar SKS. Patienter med karotisförkalkningar i PB uppvisar fler riskfaktorer och är oftare drabbade av hjärt-kärlsjukdomar än patienter utan karotisförkalkningar i PB. Majoriteten av patienter med SKS uppvisar karotisförkalkningar i PB och nära 100% av utopererade karotisplack innehåller kalk. Förkalkningsmängden påverkar inte möjligheten att upptäcka karotisförkalkning i PB. Förkalkningsmängd och specificerade radiografiska utseenden hos karotisförkalkningar i PB förutsäger inte SKS bättre än definitionen "förkalkning ja eller nej". Dessa parametrar kan således inte användas till att förfina urvalet bland patienter som uppvisar karotisförkalkning i PB mot högre andel patienter med SKS. Individer med karotisförkalkningar i PB bör uppmanas konsultera vården för undersökning av eventuella risk faktorer för hjärt-kärlsjukdom.

Abbreviations and Glossary

ACST	Asymptomatic Carotid Surgery Trial
CAC	Carotid artery calcification seen in panoramic radiograph
CBCT	Cone Beam Computed Tomography
CEA	Carotid endarterectomy
CT	Computed tomography
CT-angio	Computed tomographic angiography
FR	Frontal radiograph
Moderate SCS	Significant carotid stenosis with 50-69% luminal reduction
NASCET	North American Symptomatic Carotid Endarterectomy Trial
Nonstenotic carotid plaque	Atherosclerotic carotid plaque with 0-49% luminal reduction
PR	Panoramic radiograph
SCS	Significant carotid stenosis comprised of a large atherosclerotic carotid plaque. In this thesis defined as a carotid stenosis that reduces the carotid lumen with $\geq 50\%$
Severe SCS	Significant carotid stenosis with 70-99% luminal reduction
TIA	Transient ischemic attack

Original papers

This doctoral thesis is based on four original papers that in the text are referred to by their Roman numerals I-IV:

- I.** Johansson EP, Ahlqvist J, Garoff M, Karp K, Levring Jäghagen E, Wester P. Ultrasound screening for asymptomatic carotid stenosis in subjects with calcifications in the area of the carotid arteries on panoramic radiographs: a cross-sectional study. *BMC Cardiovascular Disorders* 2011; 11:44.
- II.** Garoff M, Johansson E, Ahlqvist J, Levring Jäghagen E, Arnerlöv C, Wester P. Detection of calcifications in panoramic radiographs in patients with carotid stenosis \geq 50%. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2014; 117:385-391.
- III.** Garoff M, Johansson E, Ahlqvist J, Arnerlöv C, Levring Jäghagen E, Wester P. Calcium quantity in carotid plaques: detection in panoramic radiographs and association with degree of stenosis. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; 120:269-274.
- IV.** Garoff M, Ahlqvist J, Levring Jäghagen E, Johansson E, Wester P. Carotid calcification in panoramic radiographs – radiographic appearance and the degree of carotid stenosis. Accepted.

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1 Introduction

Observation of carotid artery calcification (CAC) in panoramic radiographs (PR) was initially reported in 1981 [1]. At that time, researchers concluded that CACs in PRs were signs of a progressive atherosclerotic process that may indicate stenosis within the internal carotid artery. Thereby, the findings could indicate an increased risk for cerebrovascular events, including stroke [1].

Dental researchers have different opinions regarding the interpretation of CACs in PRs. Some question the relevance of these findings and others claim that PRs can be used to identify individuals at risk for stroke [2-4]. The fact that such divergent opinions exist implies that more research has to be conducted within this area, research that focus on analysis and interpretation of CACs observed in PRs.

1.1 Atherosclerosis

CACs in PRs are signs of atherosclerotic disease [1]. Atherosclerosis is a multifactorial and complex disease that proceeds for years [5]. Atherosclerosis is the major underlying cause for stroke and coronary heart disease that are the leading causes of death and disability worldwide [6, 7]. The disease develops in the walls of median- and large- sized arteries facilitated by pro-atherogenic risk factors as: hypertension, atrial fibrillation, smoking, hyperlipidemia, unhealthy diet, alcohol abuse, obesity, physical inactivity, diabetes, depression and psychosocial stress [5, 7, 8]. Vessel curvatures and arterial branches (e.g. the carotid bifurcation) are predisposed sites for initial growth [5, 9, 10]. At these sites the vessel wall is exposed to multiple biomechanical forces leading to vessel wall alterations that facilitate progression of the atherosclerotic lesion [5, 9].

High blood concentration of low density lipoprotein (LDL) is regarded as one of the cornerstone for atherosclerotic lesion development [5, 11]. Lesion development is initiated when LDLs accumulate within the intima - the thin, inner layer of an artery facing the bloodstream [5]. Accumulated LDLs initiate an inflammatory response and inflammatory cells (e.g. macrophages) are recruited into the intima where they engulf LDLs. These fat-laden macrophages (foam cells) accumulate and develop lipid pools that promote development of calcification [5, 9, 10]. As the lesion grows, the arterial wall remodels at the site of the lesion in order to maintain its luminal diameter. This process is termed arterial outward or positive remodeling. When the lesion exceeds approximately 40% of the potential lumen area the capacity

for positive remodeling is surpassed and luminal diameter decreases - the lesion becomes stenotic [9, 12]. Positive remodeling is the reason that a majority of advanced plaques do not cause significant luminal narrowing which make stenotic plaques relatively rare [13].

The fatty atherosclerotic plaque constitutes of highly thrombogenic material that is covered and separated from the bloodstream by a fibrous cap. By mechanisms not fully understood the fibrous cap can rupture and the thrombogenic material is exposed to the bloodstream initiating immediate thrombosis [13]. The thrombus covers the site of rupture from where it bulges into the lumen. Thrombus *per se* does not necessarily lead to clinical symptoms and the ruptured cap can heal silently [7, 13]. Clinical symptoms occur when the thrombus causes local vessel occlusion and/or dislodges as an embolus that occludes a smaller and more distal placed artery [7, 13]. A thrombus situated in the coronary arteries can cause myocardial infarction and if situated in a vessel that supplies the brain with blood, it can cause a stroke.

1.2 Stroke

Stroke is defined as a sudden developed symptom of acute neurological dysfunction that lasts more than 24 hours with presumed vascular disturbance in the blood flow to the brain [14]. If neurologic dysfunctions are restored within 24 hours the term transient ischemic attack (TIA) is used [15, 16]. Worldwide, stroke is the second most common cause of death and consumes 2-4% of total health-care costs [17]. In developed countries stroke is the most common cause for disability [7, 17, 18]. The most important risk factor for stroke is high blood pressure [8]. Recent trends of declining stroke incidence in developed countries are largely ascribed to blood pressure lowering efforts [19]. However, age is also an important risk factor. More than half of all strokes occur in people older than 75 years and an increase in stroke incidence is predicted due to aging population [19, 20]. Other risk factors for stroke are e.g. heredity, smoking, unhealthy diet, physical inactivity, alcohol abuse, stress, atrial fibrillation and diabetes [7, 8]. Stroke care and prevention is continuously improved due to progress in diagnostics, medication, knowledge, public information and establishment of specialized stroke care units [17].

The brain is in constant need of oxygen and glucose and requires a constant blood flow to obtain its functionality. A blood flow reduction below certain thresholds in a brain region leads to focal neurological symptoms (e.g. hemiparesis, aphasia and hemianopia) and often devastating long-term consequences. The duration and the degree of blood flow reduction

determine whether the damage will be irreversible [17, 21]. Stroke can be divided into hemorrhagic and ischemic stroke. Hemorrhagic stroke constitutes around 15% of all strokes and is caused by a ruptured artery that either surrounds (subarachnoidal) or is situated within (intracerebral) the brain [19, 22]. Ischemic stroke constitutes around 85% of all strokes and is caused by a clot or other obstruction/occlusion within an artery supplying the brain [17, 19, 22]. Brain injury, following arterial obstruction, is a dynamic process where the degree of ischemic injury is dependent on the severity of local cerebral blood flow impairment [21]. Brain tissue affected by severe blood flow impairment progresses within minutes and hours to infarction (irreversible damaged) and is termed the ischemic core. Brain tissue affected by moderate blood flow impairment, surrounding the ischemic core, turn ischemic but can maintain its structural integrity for a few hours. This territory is termed the ischemic penumbra; an ischemic territory with healing potential amenable for therapeutic intervention [21, 23]. (Figure 1) The ischemic penumbra is the target for stroke therapeutic intervention and the reason for stroke being a medical emergency. Immediate and appropriate medical intervention is associated with neurological improvement and recovery [17, 24, 25].

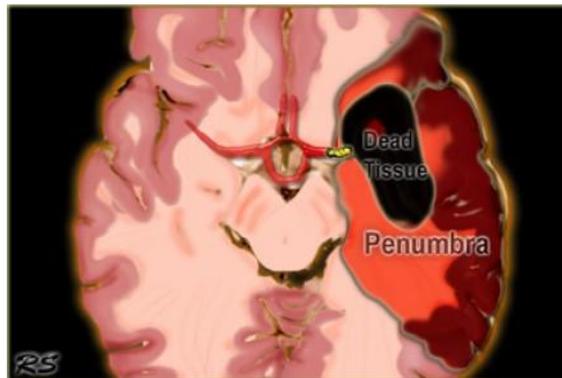


Figure 1. Schematic illustration of ischemic core (black) surrounded by penumbra (red) after occlusion of the medial cerebral artery. With permission from the Radiology Assistant (section: Neuroradiology written by Majda Thurnher).

In ischemic stroke, vessel obstruction in the arterial tree usually occurs due to local thrombosis (blood clot) or embolus formation (dislodged thrombus) [16, 17]. Cardiac embolism stands for approximately 30% of all clots that lead to ischemic stroke where atrial fibrillation constitutes around 20% [16, 19]. Around 10-15% of all primary ischemic strokes are associated with ipsilateral carotid stenosis > 50% [26, 27, 28]. In case of significant (50-99%) carotid stenosis the main mechanism is due to artery-to-artery embolization from the carotid stenosis region to the brain rather than an obstruction of the carotid artery blood flow [29].

1.3 Treatment of patients with carotid stenosis

Carotid stenoses signify a narrowing of the carotid artery caused by atherosclerosis. Atherosclerotic plaques that narrow the carotid lumen with $\geq 50\%$ and up to 99% are termed significant carotid stenosis (SCS) [30, 31]. From hereafter SCS refers to carotid stenosis $\geq 50-99\%$ and carotid plaques $< 50\%$ are termed nonstenotic carotid plaques. There is a somewhat arbitrary but important distinction between patients with SCS that have had and those that have not had an ischemic lesion (stroke or TIA). A patient with an ischemic event and ipsilateral SCS, identified within six months from symptom onset, is termed “symptomatic”. A patient with SCS but who never experienced an ischemic event is termed “asymptomatic” [27, 31]. This clinically based distinction of patients is also transferred to stenosis level where SCS are divided into symptomatic or asymptomatic stenoses. What makes this distinction important is the difference in risk of stroke and stroke recurrence. Due to this difference, symptomatic and asymptomatic patients receive different treatment interventions. However, all patients with SCS require so-called best medical treatment with the intention to reduce the risk for embolic events or stroke and to control the processes that facilitate atherosclerotic lesion progression [27].

1.3.1 Patients with symptomatic carotid stenosis

Besides medical treatment the risk of stroke can further be reduced with carotid endarterectomy (CEA) were the SCS (carotid plaque) is surgically extirpated. According to pooled results from three large multi-center randomized controlled trials (North American Symptomatic Carotid Endarterectomy Trial (NASCET), The European Carotid Surgery Trial (ECST) and the Veterans Affairs Cooperative Studies Program 309 (VA309)) patients with symptomatic severe SCS, defined as 70-99%, highly benefit from CEA compared with medical treatment alone (2-year stroke risk of 9% vs 26% NASCET) [32-34]. Patients with symptomatic moderate SCS, defined as 50-69%, also benefit from CEA before medical treatment but to a lesser extent (5-year stroke risk 16% vs 22% NASCET) [32, 34].

Benefit from CEA is not only dependent on the degree of stenosis but also on the time span from cerebrovascular symptom to surgery. Patients with symptomatic SCS experience a high risk of stroke (recurrent) during the first weeks after cerebrovascular symptom onset [30, 32, 33, 35]. CEA within two weeks from symptom onset of patients with severe SCS resulted in a 30% absolute 5-year risk reduction of ipsilateral ischemic stroke compared to 18% after 2-4 weeks [36]. This implies that for effective stroke prevention, quick identification of symptomatic patients with SCS is required as well as initiation of treatment [32, 33, 36].

CEA itself entails a 3-13% perioperative risk of immediate stroke or death within 30 days from surgery and the benefit of surgery is of course higher when perioperative risk is low. The perioperative risk is e.g. dependent upon the presence or absence of neurologic events and differs between men and women [37, 38]. Women experience higher risk of perioperative death than men (9% vs 7%) and CEA of symptomatic SCS in women performed > 2 weeks from randomization reveals no significant benefit compared to best medical treatment [36, 39]. According to the guidelines from The European Society for Vascular Surgery, CEA is recommended in symptomatic patients with SCS > 50%, if the perioperative risk is < 6% and performed within 2 weeks from last symptoms [40]. (Figure 2)

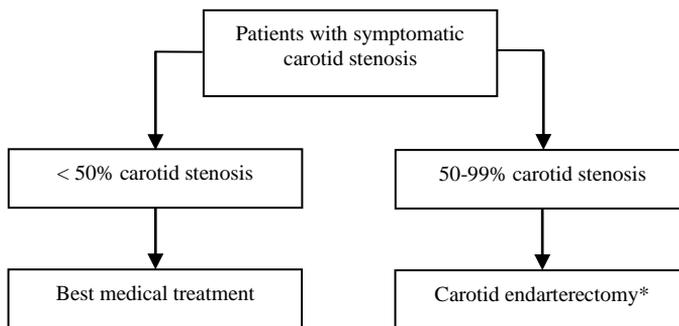


Figure 2. Treatment recommendations for patients with symptomatic carotid stenosis according to the guidelines from The European Society for Vascular Surgery.

*Preferably within 2 weeks from symptom onset and with perioperative risk < 6%.

“Best medical treatment” alone is recommended in patients with nonstenotic symptomatic carotid plaques since CEA in these groups resulted in a 20% increased risk of disabling stroke or death [25, 36]. Carotid stenoses of 100% (occlusions) entail no risk of further distal embolization and reconstructive surgery is therefore unnecessary [27].

1.3.2 Patients with asymptomatic carotid stenosis

Whilst the choice of treatment strategies in patients with symptomatic SCS is well established among health providers, treatment strategies for patients with asymptomatic SCS are strongly debated. Asymptomatic moderate SCS have a prevalence of 4% and asymptomatic severe SCS have a reported prevalence of 2-3%. Men are generally more affected than women and the prevalence of asymptomatic SCS increases with age in both men and women [41, 42].

Asymptomatic SCS are associated with ischemic events. The annual risk of stroke in patients with asymptomatic SCS < 75% is less than 1% but increases to 2-5% in patients with carotid stenosis > 75% [43, 44].

The Asymptomatic Carotid Surgery Trial (ACST) (a large multi-center randomized controlled trial for patients with asymptomatic SCS) showed at 5- and 10-year follow up an absolute risk reduction favouring CEA before best medical treatment in patients with asymptomatic severe SCS [45, 46]. The risk of any stroke at 5- and 10-years follow up respectively, (excluding 3% perioperative risk of stroke or death) was 4 and 11% in the surgery group vs 10 and 17% in the medically treated group. Protective effects were significant for men and women younger than 75 years of age at time of study entry; although, women experienced a smaller benefit compared to men [45, 46]. Patients that only received medical treatment showed over time a greater risk for stroke compared to the surgically treated group. The surgically treated group experienced an initial greater risk for stroke due to the perioperative risk of 3%, but the stroke risk then declined 1% annually. Women did not achieve statistical significant benefit until three years after surgery but women revealed a greater benefit from surgery at longer follow-up compared to men. Men revealed a significant benefit already after 1.5 years after surgery. Therefore, as long as perioperative risk remains low, CEA is more beneficial in asymptomatic (male) patients with long life-expectancies (> 10 years) than in those with short life expectancies [45]. According to the guidelines from The European Society for Vascular Surgery, CEA is recommended in men < 75 years with asymptomatic severe SCS if the perioperative risk is < 3%. CEA in women should only be performed if they are at good health [40]. (Figure 3)

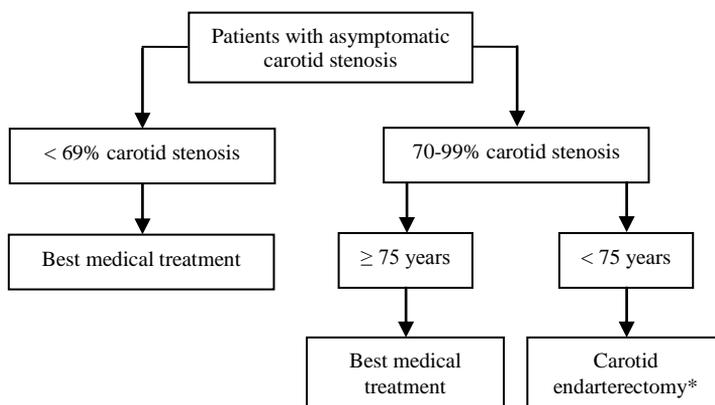


Figure 3. Treatment recommendations for patients with asymptomatic carotid stenosis according to the guidelines from The European Society for Vascular Surgery.

*Perioperative risk < 6%

1.3.3 Asymptomatic carotid stenosis – future aspects

The reported benefit of CEA in patients with asymptomatic SCS compared to medical intervention alone is currently heavily debated. When the asymptomatic carotid surgery trials were performed the annual stroke risk in the medically treated group was 2-3% [45, 47]. Due to recent improvements in pharmacologic medication (e.g. statins and oral anticoagulants in case of atrial fibrillation) and improved control of pro-atherogenic risk factors (e.g. blood pressure and diabetes), the current annual stroke risk is estimated to less than 1% and benefit of carotid surgery is therefore questioned [18, 25, 48]. Further, the reported benefit of CEA compared to medical treatment alone is highly dependent on a low perioperative risk (< 3%) that might be difficult to achieve in general surgical practice. The role of CEA in patients with asymptomatic SCS is being reinvestigated in one major ongoing trial, the Asymptomatic Carotid Stenosis Stenting vs Endarterectomy Trial (CREST-2), and it has been suggested that current best medical treatment results in lower stroke risk than CEA.

The prevalence of patients with asymptomatic severe SCS is low (2-3%) and screening of a population for asymptomatic SCS is not considered cost-effective [42, 49]. Asymptomatic SCS can be identified on the contra-lateral side to a symptomatic SCS, during preparation for e.g. coronary bypass surgery, when a carotid bruit is noticed during examination of the neck with stethoscope or during general health screening [27]. Most of the patients with asymptomatic SCS remain asymptomatic and only few benefit from surgical intervention. Even though SCS is considered a cause for a large proportion of ischemic stroke events (10%) the possibility to make a big impact on the total stroke burden by prophylactic surgical intervention of all patients with severe asymptomatic SCS is fairly low and some even consider it to be cost-ineffective [50]. Previous calculations, where directed screening for asymptomatic SCS was considered cost-effective in populations with prevalence of 5-20% and low perioperative risk (< 5%), have to be reconsidered [49]. In fact, to date there is no method available that on population or patient level adequately can identify those individuals with asymptomatic SCS that have a higher than average annual stroke risk and who in the end could benefit from surgical intervention [48, 51]. General vascular risk factors (e.g. hypertension or cardiac disease) and morphologic risk stratification of atherosclerotic plaque characteristics are presently not sufficient to define a specific high-stroke-risk subgroup of asymptomatic patients [9, 52]. Stroke prophylactic management of patients with asymptomatic SCS is yet unclear.

However, the presence of SCS represents an advanced stage of atherosclerotic disease. Given the systemic nature of atherosclerosis,

patients with carotid atherosclerosis frequently have atherosclerosis elsewhere in the arterial tree e.g. in the aorta, coronary arteries, and peripheral arteries [53, 54]. Carotid atherosclerosis is an indicator of increased risk of nonstroke vascular event and patients with asymptomatic SCS are at greater risk of myocardial infarction and death of cardiac disease than stroke [51, 55, 56]. Further, individuals with nonstenotic carotid plaques reveal an increased risk of combined vascular events in comparison to individuals without carotid plaques [57]. Recent guidelines for cardiovascular disease prevention recommend intensive medical therapy for individuals with asymptomatic SCS [56]. If this recommendation can be applied for individuals with nonstenotic carotid plaques has to be further analysed. Highly intensive medical intervention in patients with nonstenotic carotid plaques might in the future be considered cost-effective.

1.4 Diagnosis of carotid stenosis

Conventional angiography or digital subtraction angiography is still considered the “gold standard” for diagnosing SCS [58]. Conventional angiography is a two-dimensional technique that requires direct intra-arterial contrast injection in the common carotid artery and multiple orthogonal projections. The area of the stenotic lumen can be visualized and blood flow dynamics within the depicted area can be estimated. This method has several disadvantages – it is invasive, expensive, time consuming and entails risk for neurological complications that reduce the potential benefit of therapeutic interventions [59]. Further, conventional angiography requires skilled operators making the method less readily available and puts patients at risk for delayed treatment insertion.

Due to the disadvantages of conventional angiography substantial interest is shown towards other carotid imaging techniques that are non-invasive, such as carotid (Doppler) ultrasound, computed tomographic angiography (CT-angio) and magnetic resonance angiography. Carotid ultrasound is inexpensive, easily available and free of ionizing radiation but the technique shows high inter-observer variability and artefacts from calcified plaques can hinder diagnosis assessment. It is recommended that criteria for stenosis assessment with carotid ultrasound are locally validated [60]. High frequency sound waves enable measurement of flow velocities in the stenotic area that can be converted into degrees of luminal reduction. Further, carotid ultrasound can help to reveal plaque localisation and plaque structures associated with neurologic events [58]. Carotid ultrasound has a high reported sensitivity (approximately 90%) and specificity (approximately 85%) in detecting severe angiographic SCS; however, the ability for carotid ultrasound to diagnose moderate SCS is less sensitive [60]. The low false-

negative rate makes carotid ultrasound a suitable screening test and in many centres it is the primary choice of modality for diagnosing severe SCS.

If the carotid ultrasound examination is inconclusive, confirmatory examinations as CT-angio can be used in addition [61]. CT-angio enables rapid data acquisition after injection of an intra-venous contrast agent. Images with high resolution are obtained and axial image reformation possibilities permit stenosis measurement comparable to those performed in conventional angiography. CT-angio has a high reported specificity (approximately 95%) in detecting severe angiographic SCS but compared to carotid ultrasound, a lower sensitivity (approximately 77%) [58, 60]. The low false-positive rate makes CT-angio a good confirmatory test. Negative aspects with CT-angio are that the examination uses ionizing radiation and artifacts from calcified atherosclerotic plaques can reduce image quality.

Contrast enhanced magnetic resonance angiography (CEMRA) is marginally more accurate in detecting angiographic severe SCS than carotid ultrasound and CT-angio [60, 61]. CEMRA does not include ionizing radiation and can polish treatment strategies since it can identify specific atherosclerotic plaque features associated with neurological events [58]. CEMRA is not used in the studies included in this thesis and therefore not further mentioned.

1.5 Panoramic radiography

The panoramic radiographic technique is developed to specifically depict the maxillomandibular region in a 2-dimensional image. (Figure 4) Panoramic radiographic examinations are performed on a daily basis in dentistry for various odontological reasons to get an overview of the teeth and jaws. Both children and adults are examined with this rotational technique that often serves as a complement to intraoral examinations.

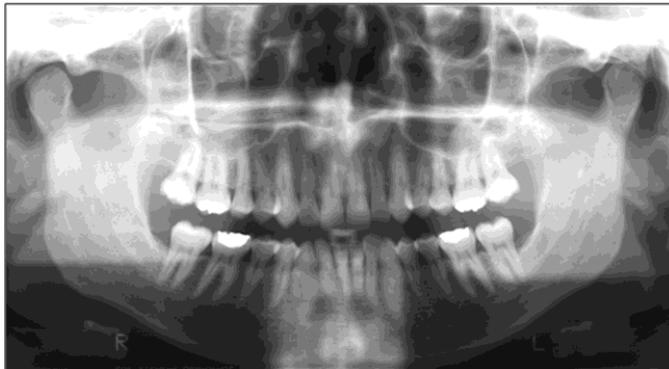


Figure 4. Panoramic radiograph.

Today, panoramic machines are commonly available in general practise. The technique is mostly digital and some machines can be upgraded to 3-dimensional imaging. The process generating panoramic images is complex and users need to be aware of the physical principles behind and the limitations that come along with this technique. This knowledge is important in order to be able to perform adequate exposures and correctly interpret and evaluate the information presented in the PR.

1.5.1 Functional principles

During exposure, the x-ray source and detector holder rotate in the horizontal plane around a centrally placed object (the head of the patient). During this rotation the detector (film or phosphor plate) moves in the opposite direction relative to the beam. (Figure 5)

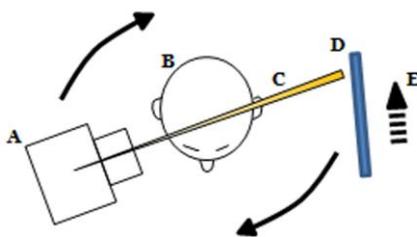


Figure 5. Rotational movement during exposure of both x-ray source (A) and detector (D) around the centrally placed head of the patient (B). During rotation the detector (D) moves in the opposite direction relative to the beam (C) as indicated by the arrow (E).

In equipments using direct digital acquisition, the effect of this movement is achieved by data handling. The rotation in the horizontal plane generates a separate functional focus called “effective focus” and it is situated at the beams rotation center. In the vertical dimension the x-ray source serves as the functional focus. The effective focus at the beams rotation center is positioned closer to the object than the x-ray source. The two different foci lead to incongruent magnification factors in the horizontal and vertical dimension defined by the ratio of the focus-to-detector distance and focus-to-object distance. By altering the speed of the detector relative to the beam, the shape and position of the sharp plane is determined. In the sharp plane the horizontal and vertical magnification factors are the same. Objects situated in this specific plane are depicted with minimum distortion and unsharpness. Distortion and unsharpness of objects increase on a continuous scale in both directions from the sharp image plane. The thickness of the so-called sharp image layer, or focal trough, is based on the accepted magnitude of unsharpness. The grade of distortion and motion unsharpness is more pronounced in the anterior region of the jaws than in

the posterior region and is more accentuated towards the beams rotation center than towards the detector.

Anatomy situated outside the focal trough due to either incorrect positioning of the patient, or to deviant anatomy compared with the averaged sized jaw will be depicted with varying degree of distortion and unsharpness. (Figure 6) For these reasons absolute measurements of objects in PRs must be interpreted with caution and the interpreter has to be aware of the diagnostic pitfalls that occur in panoramic radiography [62].

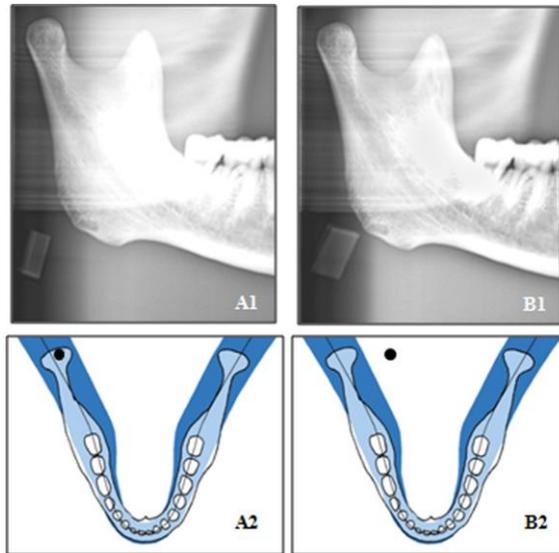


Figure 6. Panoramic radiographs of mandible with radiopaque object (a rectangular piece of aluminium) situated in the area where carotid artery calcifications can be depicted. Beneath, axial illustration of a mandible with a sharp image plane (blue area) superimposed and a black dot illustrating the position of the object in relation to the sharp image plane. In A1 and A2 the object is positioned within the sharp image plane. The object is depicted with minimum distortion (A1). In B1 and B2 the object is positioned medial to the sharp image plane. The resulting image of the object (B1) becomes distorted (asymmetrically enlarged).

1.5.2 Prevalence and differential diagnosis of carotid artery calcifications

The arteria carotis communis bifurcates approximately at the level of the 3rd or 4th cervical vertebrae into the internal and external carotid artery [63]. The carotid bifurcation is a predisposed site for development of atherosclerotic lesions and calcification within these lesions is a common feature that manifests at early middle age and progresses with increasing age [5, 9, 10]. Beside teeth and jaws, PRs also depict parts of the neck. Depending on patient anatomy and patient position in the panoramic machine, the panoramic image can include the area down to or beyond the

4th cervical vertebrae. Thus, calcified carotid atherosclerotic lesions, defined as carotid artery calcifications (CAC), can be observed in PRs. (Figure 7)

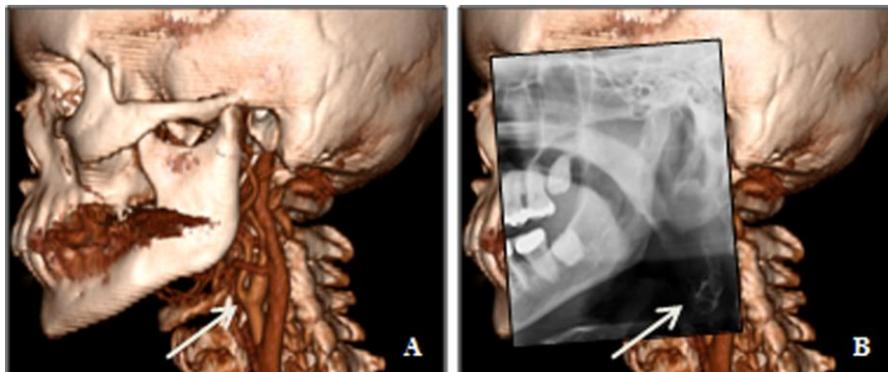


Figure 7. (A) Computed tomographic angiography (CT-angio) 3-D reformation illustrating the area of the left carotid bifurcation (arrow). (B) Cut-out of a panoramic radiograph superimposed on the CT-angio examination illustrating carotid artery calcification in the area of the left carotid bifurcation.

However, CACs have to be differentiated from other calcified anatomical or pathological structures that can appear within the same region, e.g. calcified stylohyoid ligaments, calcified superior horn of the thyroid cartilage, the triticeous cartilage, tonsilloliths, sialoliths or calcified lymph nodes [64-68]. (Figure 8)



Figure 8. Panoramic radiograph illustrating carotid artery calcifications (CAC) on the patients right and left side at the level for the third (C3) and fourth (C4) cervical vertebrae just below the mandibular angle (M). Other calcified structures that appear in the same region are the calcified thyroid cartilage (Th), calcified triticeous cartilage (Tr) and the hyoid bone (Hy).

Anterio-posterior radiographic projections (frontal radiographs) have been used to verify that a calcification observed in the area of the carotid artery in PRs actually is positioned within the carotid artery [68]. The projection of a frontal radiograph (FR) is nearly orthogonal towards the region were the CACs are depicted in PRs. FRs have been used as an aid in the differentiation

of CACs from other calcified anatomical or pathological structures that appear within the same area in the PR [68]. (Figure 9)

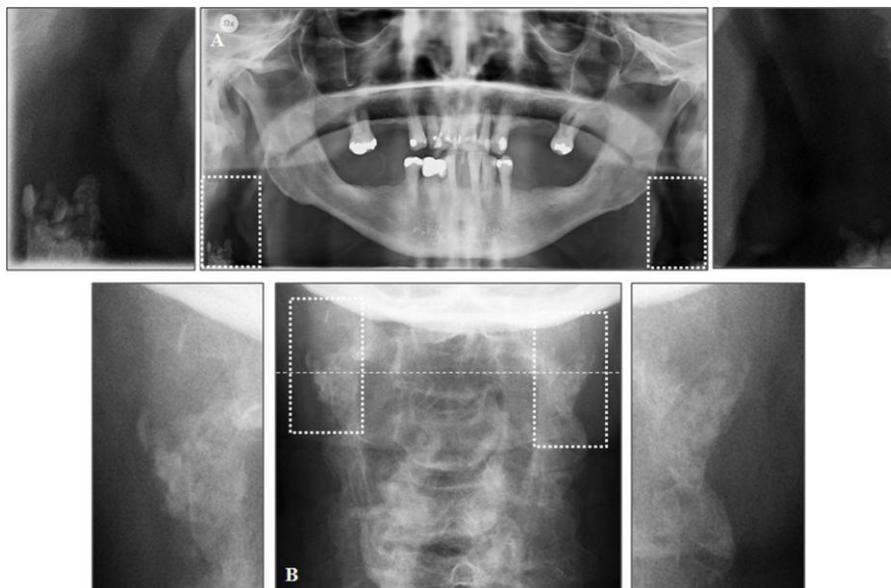


Figure 9. (A) Panoramic radiograph (PR) illustrating bilateral carotid artery calcifications (CACs) verified in the (B) frontal radiograph (FR). The horizontal line in the FR represents the approximate inferior border of the PR and illustrates in this case that most of the CACs are not depicted in the PR.

CACs in PRs have in a general population a reported prevalence of 2-5%. Prevalence of CACs in PRs increases with age [69-73]. Even higher prevalences have been reported in populations treated with therapeutic irradiation (21%) or in populations with osteoradionecrosis (28%), diabetes mellitus type 2 (36%), postmenopausal women and dilated cardiomyopathy (33%) [74-78].

1.5.3 Carotid artery calcifications in relation to carotid stenosis and vascular risk factors

As previously described, screening of a general population for asymptomatic SCS is not cost-effective due to low prevalence. However, screening for SCS in sub-populations with higher prevalence (5-20%) of asymptomatic carotid stenosis is (yet) considered cost-effective given that the perioperative risk is low (< 5%) [49].

According to two earlier studies, performed on populations in dentistry care, CACs in PRs coincided with ipsilateral SCS in 21 respectively 50% of neck sides. SCS were determined with carotid ultrasound [71, 79]. Based on these findings it has been proposed that individuals with CACs in PRs constitute a

subgroup that have a higher prevalence of asymptomatic SCS compared to a general population and that carotid ultrasound screening of that subpopulation might be justified [3, 71]. The study samples were though relatively small (n = 20 and 65 respectively). In addition, more than 72% of the participants were men and both studies included individuals > 75 years of age who are not eligible for asymptomatic carotid surgery [40]. It is uncertain whether this high prevalence represents the prevalence in a general dentistry population including men and women with equal proportions that at the same time fulfill the criteria for asymptomatic carotid surgery (e.g. < 75 years and at fairly good health).

Individuals with nonstenotic carotid plaques have an increased risk of combined vascular events in comparison to individuals without carotid plaques [57]. Whether this increased vascular risk can be applied to patients that reveal incidental findings of CACs in PRs has to be further investigated. Some retrospective studies have described CACs in PRs to be a risk factor or risk marker for vascular events [72, 80-82]. However, the studies fail to substantiate their conclusion since they do not provide a control group without CACs in PRs.

The sensitivity of PRs in detecting individuals with SCS by means of CACs can be obtained by performing PR examinations on populations with verified SCS. The sensitivity is dependent on how often carotid plaques are calcified and the position of the CAC in relation to the depicted area. It has been reported that in 37% of male patients that had experienced a cerebrovascular accident, PRs revealed CACs. It was, however, unknown if the patients had SCS [83]. In another study, 70% of patients with severe SCS revealed ipsilateral CACs in PRs prior to CEA. Nearly 80% of the participants were men. The same study also reported calcification in all of the extirpated carotid plaques, and all neck sides with verified calcified carotid plaques (neck sides with calcified SCS) presented CACs in the PRs. Analysis regarding the location of missing calcified SCS with respect to the depicted panoramic field was not necessary since all calcified extirpated carotid plaques were depicted in the PRs and individuals with SCS < 70% were not included [84].

1.5.4 Radiographic appearance of carotid artery calcifications

An observer analyzing a PR might be more prone to associate prominent CACs with SCS than small CACs. It would be useful to determine if radiographic appearance as e.g. the size and shape of CAC as seen in the PR could identify a subpopulation with higher prevalence of SCS.

The relationship between calcification quantity within atherosclerotic carotid plaques and degree of SCS > 40% has been analysed with CT. Varying correlations from $r = 0.04$ to 0.65 have been reported and calcified carotid plaques are more associated with asymptomatic compared to symptomatic individuals [85-88]. There has been an attempt to quantify CACs in PRs to study the relationship between area of CAC and degree of SCS. A weak positive correlation was found [89]. As previously described, absolute measurements in PRs are not recommended due to the complex object distortions that occur when the object of interest is positioned outside the sharp image plane [62]. (Figure 6) Further, it is not guaranteed that the whole CAC is depicted in the PR leading to incorrect assumptions or correlations regarding the potential importance of the size of the CAC. (Figure 9) Other methods, than direct measurements in PRs, are required that can address the significance of size of CACs in PRs in relation to SCS. Present research results does not provide a reliable answer to whether large sized CACs in PRs are more associated with SCS compared to small sized CACs.

Due to the fact that PRs not always depict the full extent of CACs it might be better to analyze whether there are any radiographic appearances of CACs that are more related to neck sides with SCS. CACs have in the literature been described as nodular, verticolinear, irregular and heterogeneous radiopacities that sometimes appear as two parallel and vertical lines [64, 65, 71, 90]. It can be anticipated that two parallel situated CACs observed in PRs also represent contralateral calcifications within the carotid artery and that these calcifications are associated with an atherosclerotic soft tissue mass. The chance for luminal reduction and increased prevalence of SCS could therefore be higher in populations revealing such CACs in PRs. To date, there are no studies that have investigated CACs radiographic appearance in relation to neck sides with SCS.

2 Aims

This thesis comprises four studies (I-IV). Study I and II have the overall aim to analyze the significance of CACs in PRs to identify patients with SCS. Study III and IV have the overall aim to investigate if it is possible to refine the selection of patients with CACs in PRs towards improved positive predictive value (PPV) for SCS detection by utilising size and different radiographic appearances of CACs in PRs.

The specific aims for this thesis were:

- I.** To determine how often odontologically examined patients with CACs in PRs reveal SCS in carotid ultrasound examinations and whether they reveal a higher burden of atherosclerotic disease compared to patients without CACs in PRs.
- II.** To analyze how often extirpated carotid plaques with SCS are calcified and how often PRs disclose these calcifications by means of CACs.
- III.** To determine if calcium volume in extirpated carotid plaque is associated with degree of SCS and if calcium volume influences the possibility to detect CACs in PRs.
- IV.** To analyze if specified categories of radiographic appearance of CACs in PRs can be used to improve PPV for SCS detection among odontologically examined patients with CACs in PRs.

3 Participants and methods

All studies are cross-sectional and all study participants were prospectively and consecutively sampled between August 2007 and Januari 2011 at the Department of Oral and Maxillofacial Radiology, Umeå, Sweden. All studies complied with the Helsinki declaration and were approved by the Regional Ethical Board in Umeå (Dnr 07-004M).

The Department of Oral and Maxillofacial Radiology examines patients of all ages referred for different odontologic reasons. Annually about 2000 PRs are performed. Approximately 50% of all PR examinations are performed on patients ≥ 18 years of age.

Umeå Stroke Center has a well-established stroke care unit. All patients with suspected SCS and potential eligibility for carotid surgery are examined with carotid ultrasound at the Department of Physiology.

3.1 Participants

The study population comprised two main groups defined as Group A and Group B. Group A comprised odontologically examined patients with CACs in PRs referred for carotid ultrasound examination. Group B comprised patients from Stroke Center with SCS examined with PR.

Study I and IV included participants from Group A. Study II, III and IV included participants from Group B.

3.1.1 Participants in Study I (Group A)

In Study I, 1182 patients of 18-74 years of age were examined with PR at the Department of Oral and Maxillofacial Radiology. Those that revealed CACs in the PR were further examined with a FR of the neck in order to confirm that the CAC in the PR was positioned in the area of the carotid arteries in the FR as well. The FR was performed, in accordance to previous literature, to increase the possibility to make a correct interpretation [68]. Age and sex were recorded for all 1182 patients including the reason for referral.

Participants in Study I fulfilled following inclusion criteria:

- age: 18-74 years
- CACs in PR with verified CACs in the FR.
- eligible for asymptomatic CEA, i.e. excluding individuals with cancer or other serious co-morbidities that might lead to short life expectancy or increased perioperative risk
- no history of cerebrovascular event defined as stroke or TIA
- informed consent

All participants of the study group in Study I were referred to the Department of Physiology for carotid ultrasound examination. Medical records were reviewed for cardiovascular events and risk factors. For comparison, an age and gender matched reference group was randomly selected among the patients without CACs in PRs. The cardiovascular medical background of the reference group was assessed with a questionnaire. This group was not examined with carotid ultrasound. (Figure 10)

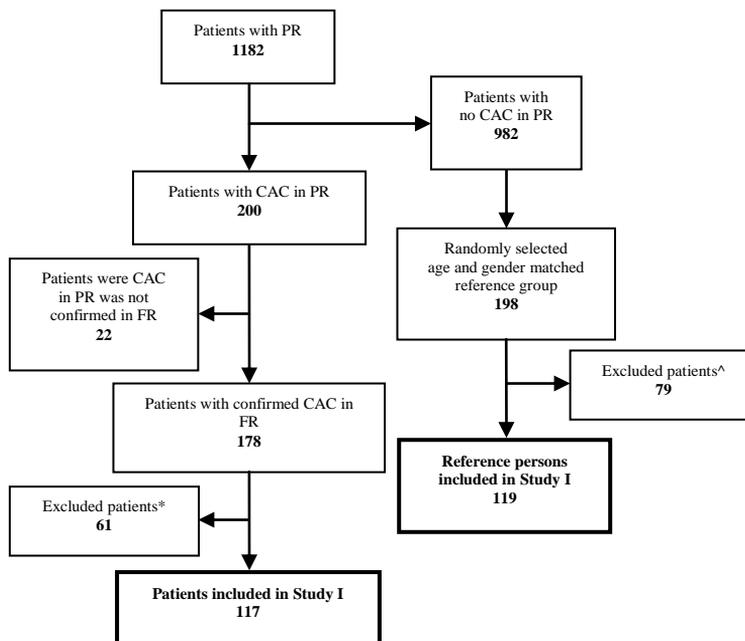


Figure 10. Flow chart of patients included in Study I. The patients had to present carotid artery calcifications (CAC) in panoramic radiographs (PR) that were confirmed in frontal radiographs (FR). The reference group was randomly selected among patients without CACs in PRs.

^ Excluded due to declined participation (59), cancer (10), previous stroke/transient ischemic attack (8), death (2)

* Excluded due to cancer (24), previous stroke/transient ischemic attack (15), serious co-morbidity (8), no informed consent (7), missed (6), transient visit (1)

The study population in Study I was collected from August 2007 to February 2009. Referrals of additional patients for carotid ultrasound examinations were resumed in November 2009 after analysis of the primary study results. Patients with CACs in PRs were thereafter referred for carotid ultrasound examination on regular basis but only men were included and FRs of the neck were no longer performed.

3.1.2 Participants in Study II and III (Group B)

Study II and III comprised patients registered at Stroke Center due to suspected symptomatic or asymptomatic SCS that were eligible for CEA. Consenting patients with SCS were referred from Stroke Center to the Department of Oral and Maxillofacial Radiology for PR and FR examination. Age, sex, pre-existing co-morbidities, symptomatic/asymptomatic SCS and degree of SCS were registered for all patients. The inclusion criterions differed slightly in Study II and III for the participants of Group B.

Participants in Study II were collected from August 2007 to December 2008. Study II had a pre-specified sample size of 100 consenting participants. Participants in Study II had to fulfill the following inclusion criteria:

- presence of SCS
- pre-operative informed consent
- pre-operative PR and FR
- CEA performed after the radiographic examinations

Participants in Study III were collected for one additional year (to December 2009). In addition to the inclusion criterions for participants in Study II, Study III only included patients from which extirpated carotid plaques were collected. Further, Study III included one endarterectomized patient from Study I (Group A) and one asymptomatic patient who at the time for Study II did not qualify for CEA; however, at revisit, during the time for Study III, the asymptomatic SCS had grown and the patient was then treated with CEA and the extirpated carotid plaque was collected. (Figure 11)

Extirpated carotid plaques were radiographically examined at the Department of Oral and Maxillofacial Radiology for presence and amount of calcification.

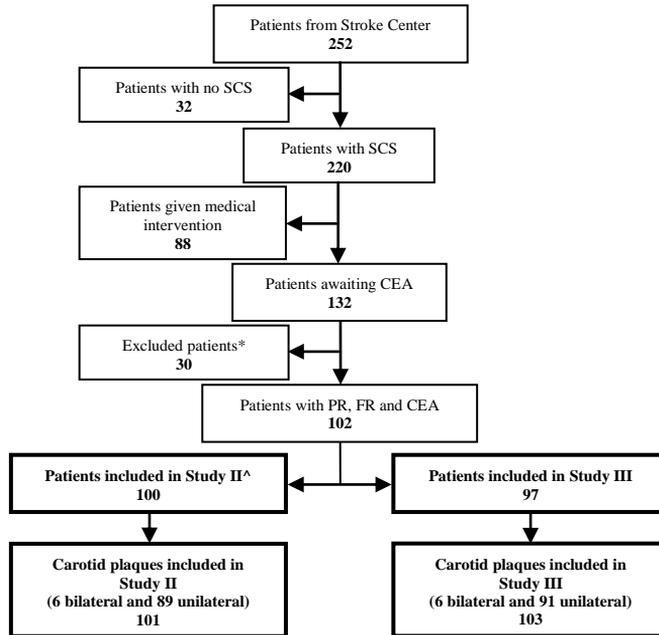


Figure 11. Flow chart of patients included in Study II and III. Patients included in Study II and III had to have significant carotid stenosis (SCS) and panoramic (PR) and frontal radiographic (FR) examination prior to carotid endarterectomy (CEA). Five extirpated carotid plaques were missed in five patients and were excluded in Study III.

*Missed (8), declined study participation (22)

^Study II excluded one patient from Study I and one patient who was not eligible for CEA at the time when selection of participants for Study II was performed.

3.1.3 Participants in Study IV (Group A and B)

PRs of all participants in Study I-III were re-evaluated in Study IV. Participants in Study IV were sampled from August 2007 to Januari 2011. All participants in Study IV had to have CACs in PRs. In some of the re-evaluated cases, CACs in PRs could not be confirmed and were therefore excluded from analysis in Study IV. FRs were not considered in the re-evaluation.

3.1.3.1 Participants in Study IV (Group A)

Besides the odontologically examined patients included in Study I, Group A in Study IV also comprised 58 consecutive sampled (male) patients with CACs in PRs that were sampled after the study period for Study I (additional sampling from November 2009 to Januari 2011). Of these, 10 were excluded (missed referral for carotid ultrasound examination (3), serious co-morbidity (6), died prior to carotid ultrasound examination (1)). Further, two patients from Study I were excluded in Study IV due to absence of CACs in PRs at re-evaluation.

Group A in Study IV comprised in total 163 patients that at re-evaluation presented CACs in PRs. (115 patients from Study I including 48 additional patients sampled after the study period for Study I.)

3.1.3.2 Participants in Study IV (Group B)

Group B in Study IV comprised 78 patients with SCS from Study II and III that at re-evaluation were defined to have CACs in PRs (CACs in PR could not be confirmed in 6 patients at re-evaluation). Group B in Study IV also included patients with SCS that only received medical intervention. (Figure 11) The medically treated group comprised 88 patients. Of these, 51 were excluded (18 declined participation, 11 revealed no CACs in PRs and 22 were missed). The medically treated group was selected during the study period for Study II. The high number of missing individuals in the medically treated group was because they did not fulfill the inclusion criteria for participation in Study II (patients had to be eligible for CEA). However, some patients in the medically treated group had performed PR since the initial treatment plan included CEA. The decision to perform CEA was though changed due to e.g. technical CEA-difficulties after radiographic examinations had been performed. The medically treated group is considered not consecutive sampled in contrast to the CEA-treated participants in study II and III.

Group B in Study IV comprised in total 115 patients that at re-evaluation presented CACs in PRs. (78 patients from Study II and III and 37 patients from the medically treated group.) (Figure 12)

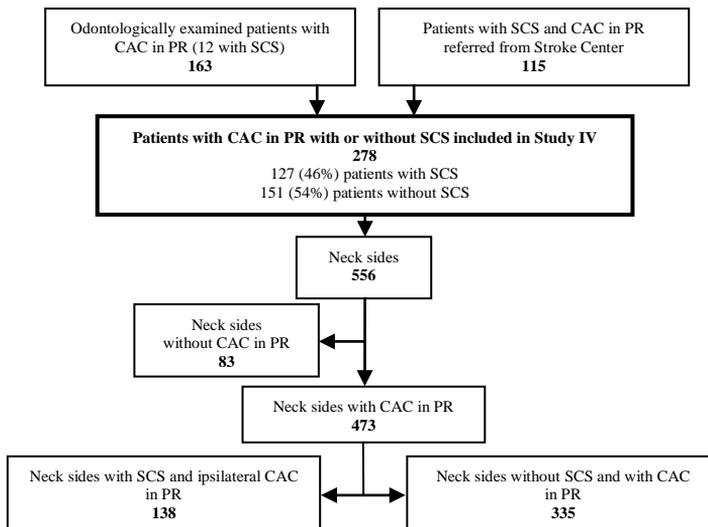


Figure 12. Flow chart of patients from Group A and B included in Study IV. Study IV includes patients with and without significant carotid stenosis (SCS) that reveal carotid artery calcifications (CAC) in panoramic radiographs (PR).

3.2 Methods

Carotid ultrasound, PR and FR examinations were performed according to standard protocols.

3.2.1 Carotid ultrasound

Carotid ultrasound examinations were performed by experienced vascular sonographers (n = 9). Flow velocities were translated into NASCET-type carotid stenosis [91]. Diagnostic validations have been performed at the Department of Physiology and all findings during the ultrasonographic examinations were confirmed with double reading before reporting [92]. For all ultrasound examinations the Siemens Acuson Sequoia 512 was used together with an 8L5 linear transducer. Plaques visible on B-mode with maximum systolic velocity in the internal carotid artery of 1.45-2.4 m/s respectively > 2.4 m/s were translated to 50-69% respectively 70-99% SCS. Internal carotid arteries with no detectable flow were diagnosed as occluded.

Inconclusive ultrasound examinations were, prior to definitive treatment decision, commonly followed up with CT-angio. CT-angio examinations were performed according to standard protocol after injection of an intravenous iodine contrast medium.

3.2.2 Panoramic and frontal radiography

The Orthopantomograph OP100 was used for all panoramic examinations performed with the P1-program. The Cranex Cephalostat was used for all frontal examinations exposed with 81 kV and 10 mA, for 0.8-1.2 s depending on patient size. For both panoramic and frontal projections, Fuji IP cassettes served as the image plate system and images were scanned with the Fujifilm FCR Capsula XL. The Schick CDR DICOM 3.5 software was used for interpretation of all images and analysis of images was performed on diagnostic computer screens.

3.2.3 Carotid endarterectomy

Surgery was performed under general anesthesia. The common, internal and external carotid arteries were carefully exposed with a longitudinal incision made in the common carotid artery extended into the internal carotid artery distal to the plaque. The plaque was carefully dissected from the arteries after division of the intimal thickening of the common carotid. This procedure leaves the adventitial layer intact and minimizes trauma to the carotid plaque. After removal, the plaque was placed in a plastic tube, primarily stored at -20 °C and then transferred to a -80 °C freezer. The

plastic tubes containing the frozen specimens were embedded in ice within a styrofoam-box during transportation from the freezer to the Department of Oral and Maxillofacial Radiology and the extirpated plaques, situated in the plastic tubes, were kept frozen during radiographic examination. (Figure 13)



Figure 13. Extirpated carotid plaque. A suture marked the internal carotid artery (in this case right arm of the plaque).

3.2.4 Radiographic examinations of extirpated carotid plaques

Extirpated carotid plaques were radiographically examined for calcifications with a digital sensor system for 2D-examinations and with cone beam computed tomography (CBCT) for 3D-examination.

The digital 2D-sensor system comprised of a Schick CDR sensor exposed with the dental radiographic machine from Focus Instrumentarium Dental at 60 kV and 0.08 seconds. When the size of the carotid plaque exceeded the size of the sensor, Fuji IP image plates were used (n = 16).

CBCT examinations were performed with the 3-D Accuitomo 170 at 60 kV, 1 mA, and 360°. Volumes of 4x4 or 6x6 cm were used depending on plaque size. All reconstructions were performed with 0.5 mm slice thickness and 0.5 mm increment. The Advantage Workstation 4.3, Volume Viewer 2 software program was used for volumetric measurements with calcification quantity defined in mm³. To compensate for partial volume effect, window width was set to zero and the threshold for maximum window level in the calcification was halved prior to all measurements.

3.3 Analysis

Analysis of radiographic examinations was performed in a room allowing ultimate dim light conditions and observers were free to adjust brightness and contrast level.

3.3.1 Panoramic and frontal radiographs

Two experienced specialists in oral and maxillofacial radiology (JA, ELJ) analysed the PRs and FRs of all participants in Group A and B. The radiographs were analysed regarding presence or absence of CACs for all patient neck sides. All CACs were differentiated from other calcified anatomical or pathological structures. Analysis was performed separate by each observer, and in cases of disagreement consensus was reached. The observers were blinded to the results of the carotid ultrasound examination and radiographic examination of the extirpated carotid plaques. Inter-rater agreements (Kappa values) were calculated in Study I, II and IV.

In Study I-III the observers were allowed to analyse PRs and FRs in the same session. FRs were excluded in Study IV and only PRs were re-evaluated for radiographic appearance of CAC.

3.3.2 Study I

3.3.2.1 Subgroups

Patients were divided into subgroups based on gender, age (< 65 years and 65-74 years), and cause of referral. The age groups used were according to the ACST-study [45]. Cause of referral was divided into subgroups defined as regular dental (dental and implant treatment), specialized dental (fractures and maxillofacial reconstruction therapy), and specialized medical (prior to medical intervention e.g. heart valve surgery). The specialized dental and medical subgroups comprised few patients and were therefore merged during analyses.

3.3.2.2 Study population and reference group

Cardiovascular events and cardiovascular risk factors were used either as a combined group or separate for each event and risk factor respectively (separate analysis is not described within this thesis). The combined group of cardiovascular events comprised previous myocardial infarction, heart failure, current angina and claudicatio (symptomatic peripheral artery disease). The combined group of cardiovascular risk factors comprised diabetes, hypertension, current smoking, blood pressure medicine, lipid lowering medicine and platelet inhibiting or anticoagulant medicine.

3.3.2.3 Carotid ultrasound examination

Prevalence of SCS among patients presenting CACs in PRs performed for odontological reasons was determined utilizing carotid ultrasound. A prevalence of SCS > 5% has been presented as cost-effective [49].

3.3.3 Study II

Patients with carotid ultrasound confirmed SCS were studied regarding calcifications in extirpated carotid plaques and signs of CACs in PRs. The analyses were performed both on neck side level and on patient level.

3.3.3.1 Analysis on neck side level

The extirpated carotid plaques, from the patients included in Study II, were analysed for presence or absence of calcification in the 2D-radiographic examinations. Findings of calcification within an extirpated carotid plaque were considered to be a finding of calcified SCS. CACs observed in PRs were correlated with findings of calcification in corresponding carotid plaques. Neck sides with CAC in PRs and ipsilateral calcified carotid plaque were considered as positive findings. Neck sides with no detectable CAC in PRs but presence of calcification in the extirpated plaque were specifically analysed regarding the position of the calcification in relation to the region depicted in vertical plane of the PR. FRs and CT-angio examinations were used for this analysis.

3.3.3.2 Analysis on patient level

Patients with uncalcified SCS could have calcified nonstenotic carotid plaques on the contralateral side. Since all patients in Study II had SCS, all patients with CACs in PRs were considered as positive findings on patient level; regardless of on which side the CACs were detected. Differences between groups of gender, symptomatic/asymptomatic SCS and age < 75 and ≥ 75 years were analysed. The age groups used were according to the criteria for asymptomatic CEA (< 75 years) [40].

The contribution of FRs as a tool to ascertain that the CAC was situated in the carotid artery in addition to PRs, was analysed on patient level.

3.3.4 Study III

In Study III analysis of PRs was restricted to neck sides with calcified extirpated carotid plaques that had been situated within the region depicted by the PR.

Calcification quantity was measured in mm³ determined by means of CBCT. The volume was correlated to degree of SCS. Differences between groups of

age, gender, and asymptomatic/symptomatic SCS were analysed. In addition, the possibility to detect CACs in PRs was related to the volume of the calcification as defined in the CBCT-examination.

3.3.5 Study IV

CACs in PRs of patients with or without SCS were studied regarding different radiographic appearances. Specified radiographic appearances were then analysed on both neck side level and patient level.

3.3.5.1 Analysis on neck side level

A separate observer (MG) first re-analysed all PRs to determine if a specific radiographic appearance of CACs predominated in neck sides with SCS. CACs were categorized into three groups:

- (1) single CAC or a tight conglomerate of several CACs
- (2) scattered CACs with at least two calcified nodules
- (3) two parallel and vertical aligned single or scattered CACs that give the impression of outlining the anterior and posterior contours of a vessel, i.e. vessel-outlining. (Figure 14)

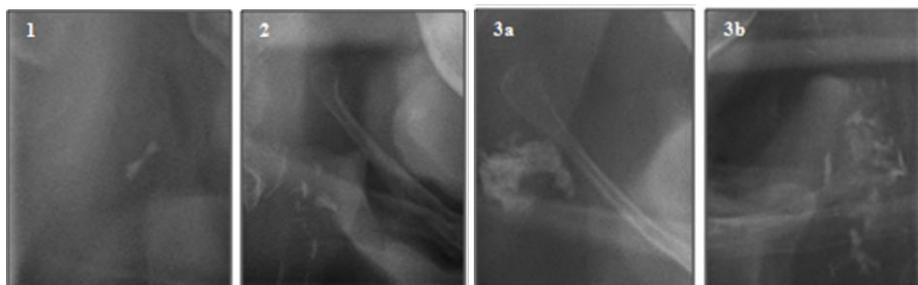


Figure 14. Specified categories of radiographic appearance of carotid artery calcifications (CAC) in panoramic radiographs: (1) single CAC or a tight conglomerate of several CACs, (2) scattered CACs with at least two calcified nodules, and (3a and 3b) parallel and vertical aligned single or scattered CACs that give the impression of outlining the anterior and posterior contours of a vessel, i.e. vessel-outlining.

The separate observer introduced two specialists in oral and maxillofacial radiology (JA, ELJ) to the specified categories. The separate observer then chose 30 PRs that represented all three specified categories for calibration purpose. After calibration, all PRs with and without CACs were mixed and re-analysed by the two observers (JA, ELJ). In case of disagreement consensus was reached.

The frequencies of the three specified categories were calculated in neck sides with and without SCS. Differences in frequency were analysed for all

participants and between men and women. Neck sides without CACs were excluded in the analysis on neck side level.

3.3.5.2 Analysis on patient level

Based on the results from the former analysis on neck side level, the specified radiographic appearances were used in different combinations to create three different subgroups of patients. The purpose of the analysis on patient level was to evaluate if any of the specified radiographic appearances or combinations of them could aid in the identification of a subpopulation in which CAC have a higher PPV (prevalence) for SCS detection compared to the conventional method where all patients with CACs, regardless of radiographic appearance, was the base for SCS prediction. Analysis on patient level was restricted to the odontologically examined participants of Group A.

3.3.6 Statistics

IBM SPSS Statistics was used for all statistical analysis.

Dependent on type of variables, differences between groups were determined with the chi-square test, the non-parametric Mann-Whitney test, the Kruskal-Wallis test or the binary logistic interaction test.

Level of significance was set at $P < 0.05$. Kappa values for interrater agreement and 95% confidence intervals (95% CI) were calculated for all PPVs in Study IV.

In Study I and IV the non-parametric binomial test was used to determine if the prevalence of SCS (Study I) or PPV (Study IV) for SCS detection was significant above a pre-specified 5%-threshold.

4 Results

4.1 Study I

During the study period, 1182 individuals were examined with PR. The mean age among the 1182 individuals was 51 years (SD 18.0, range 18-74 years), 70% were < 65 years, 52% were men and 56% of the referrals were for regular dental reasons.

CACs in PRs were seen in 200/1182 (17%) of patients. FRs ascertained the presence of CACs as seen in the PRs in 178/1182 (15%) of patients. The final study population consisted of 117 participants that were considered eligible for asymptomatic CEA if they were found to have SCS.

The mean age of the 117 study participants was 67 years (SD 5.6, range 45-74 years), which was significantly higher compared to the mean age (50 years; SD 18.1, range 18-74 years) of all the individuals without CAC in PRs, ($p < 0.001$). The interobserver agreement showed a kappa value of 0.7.

4.1.1 Subgroups

Men and women were included at equal proportions, (55% and 45% respectively, $p = 0.67$), 66% of PRs with CACs (ascertained in FRs) occurred in patients of the older age group (65-74 years of age), ($p < 0.0001$). PRs performed for regular dental reasons comprised 80% of all referrals, ($p < 0.0001$). (Table 1)

Subgroups		Study population (%) n = 117	P*
Gender	Men	64 (55)	0.67
	Women	53 (45)	
Age-group	<65	40 (34)	< 0.0001
	65-74	77 (66)	
Cause of referral	Regular dental	94 (80)	< 0.0001
	Specialized dental	6 (5)	
	Specialized medical	17 (14)	

Table 1. Frequencies of carotid artery calcifications in panoramic radiographs in different subgroups of odontologically examined participants (Study I).

* Chi-square test

4.1.2 Comparisons between study population and reference group

Combined cardiovascular events occurred in higher proportion in the study population compared to the 119 individuals in the age and gender matched

reference group without CAC in PRs (38% and 10% respectively, $p < 0.0001$). This was also the case regarding combined cardiovascular risk factors (86% compared to 65%, $p = 0.0002$).

4.1.3 Findings in carotid ultrasound examination

Carotid ultrasound examinations were performed on average within 83 days (SD 54) after the panoramic examination. Carotid ultrasound identified nine SCS in 8/117 (7%) patients in the study group, which was not significantly over the pre-specified threshold of 5%, ($p = 0.23$). All SCSs were found in men (8/64 (12.5%)), a proportion which was significantly above the pre-specified threshold of 5%, ($p < 0.01$).

Patients with CACs in PRs and with SCS were significantly more associated to have experienced any combined cardiovascular event compared to patients with CACs in PRs and with nonstenotic carotid plaques, (16% compared to 1%, $p < 0.003$). All eight individuals revealed cardiovascular risk factors.

Five of the eight men were diagnosed with moderate SCS and were offered medical intervention alone. The remaining three were diagnosed with severe SCS and were offered CEA. CEA was performed in one patient (one patient refused and one died before CEA).

Bilateral SCS were found in one of the eight patients with SCS. All SCS revealed calcification in carotid ultrasound and PRs revealed CACs in all of the nine neck sides with SCS. Among the 109 participants without SCS, carotid ultrasound identified nonstenotic calcified carotid plaques in 99% of the neck sides presenting CAC in the PR.

4.2 Study II

Study II included 100 patients that had performed CEA due to symptomatic (85%) or severe asymptomatic SCS (15%). All patients were examined with PRs and FRs prior to CEA. The average time from radiographic examination to performed CEA was 33 days (SD 50). The average time differed between symptomatic (average 26 days (SD 42)) and asymptomatic patients (average 76 days (SD 69)). Men constituted 70% of the study population and the mean age was 71 years (SD 7.4, range 52-86 years).

In 96% the degree of SCS was defined with carotid ultrasound and in 4% with CT-angio. Carotid ultrasound examinations were performed in all participants and CT-angio examinations were performed in 48 participants

as a complement. The degree of SCS, assessed with both carotid ultrasound and CT-angio, was in agreement in 95% (42/44) of cases.

The interobserver agreement regarding observations of CACs showed Kappa values of 0.88 for PRs and 0.86 for FRs.

4.2.1 Neck side level

Five extirpated carotid plaques were missed in 5/100 CEA-patients. A total of 101 extirpated carotid plaques were collected from 95 patients (6 bilateral and 89 unilateral CEAs). The 2D-radiographic examination revealed calcification in all but one (100/101 (99%)) of extirpated carotid plaques.

CACs in PRs were observed in 75/100 (75%) neck sides with ipsilateral verified calcified SCS (i.e. the 100 calcified extirpated carotid plaques). PR or FR revealed no CAC on the neck side with the uncalcified carotid plaque.

In 25/100 (25%) neck sides with calcified SCS, CACs were not observed in the PRs. The FRs and/or CT-angio examinations disclosed 19 of these 25 (76%) and revealed that all but one (18/19 (95%)) were situated below the region depicted by the PR.

4.2.2 Patient level

On patient level all 100 patients with SCS were included. In total 84/100 (84%) patients presented CAC in PRs. In 90% (76/84) of these, CAC was seen on the ipsilateral side to the SCS and in 10% (8/84) on the contralateral side. When CACs in PRs had to be ascertained by FRs (PR_{and}FR), 74/100 (74%) of patients were included. The combination PR_{and}FR excluded 10 of 84 (12%) patients when compared to the single use of PRs.

There was no significant difference in proportion regarding findings of CACs in PRs between any of the defined subgroups. (Table 2)

Subgroups		n	CAC in PRs (%)	P*
Gender	Men	70	58 (83)	0.77
	Women	30	26 (87)	
Age-group	< 75	70	57 (81)	0.70
	≥ 75	30	27 (90)	
Carotid stenosis	Symptomatic	85	71 (83)	0.38
	Asymptomatic	15	12 (80)	

Table 2. Number of panoramic radiographs (PR) presenting carotid artery calcifications (CAC) in subgroups of participants with SCS (Study II).

*Chi-square test

4.3 Study III

Study III comprised 96 patients with extirpated carotid plaques from Group B and one patient with extirpated carotid plaque from Group A/Study I. The patients had a mean age of 70 years (SD 7.5, range 52-86 years) and all were examined with PR prior to CEA. All extirpated carotid plaques were examined with CBCT. (Figure 15)

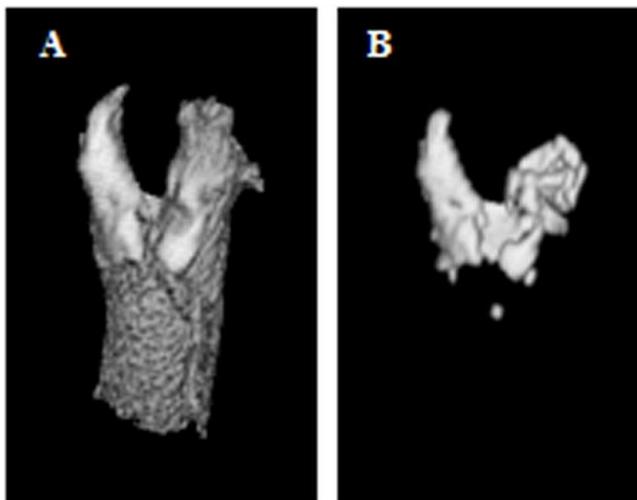


Figure 15. (A) 3D-reconstruction of extirpated carotid plaque. (B) Corresponding plaque with adjusted settings for separate visualization of calcification.

In total, 103 extirpated carotid plaques were collected (6 bilateral and 91 unilateral CEAs). Due to few SCS of 50-59% and 60-69%, these groups were merged into a 50-69% SCS-group during analysis. The degree and distribution of the 103 SCS prior CEA was as follows:

- 10 SCS degreed as 50-69% (10%)
- 28 SCS degreed as 70-79% (27%)
- 30 SCS degreed as 80-89% (29%)
- 35 SCS degreed as 90-99% (34%)

The majority of extirpated carotid plaques came from symptomatic patients (77/103 (75%)), and men (73/103 (71%)).

CBCT-examinations revealed calcification in all but one of the extirpated carotid plaques (99%). Calcification volumes ranged from 1 mm³ to 509 mm³ (median = 45 mm³, Q1 = 14 mm³, Q3 = 98 mm³). Calcification volumes were not associated to any of the defined subgroups. (Table 3)

Subgroups		n=103	Median calcification volume (mm ³)	P
Specimen	From men	73	45	0.99 [‡]
	From women	30	44	
Age-group	50-60	10	22	0.75 [*]
	61-70	39	36	
	71-80	47	49	
	81-90	7	54	
Degree of carotid stenosis	50-69%	10	62	0.59 [*]
	70-79%	28	53	
	80-89%	30	40	
	90-99%	35	33	
Carotid stenosis	Symptomatic	77	52	0.12 [‡]
	Asymptomatic	26	25	

Table 3. Median calcification volume (mm³) as measured with cone beam computed tomography of extirpated carotid plaques with SCS in different subgroups (Study III).

^{*}Mann-Whitney test

[‡]Kruskal-Wallis test

Of the 102 calcified carotid plaques, 78 were situated within the region depicted by the PR. All but one (99%) of these 78 were identified in the PR by means of ipsilateral CAC. The calcified SCSs depicted in the PRs had calcification volumes ranging from 1 to 509 mm³.

4.4 Study IV

Study IV comprised 163 odontologically examined patients from Group A (12 with SCS) and 115 patients with SCS from Group B; all 278 study participants revealed CACs in PRs at re-evaluation. The mean age was 68 years (SD 6.6, range 45-86 years) and 188/278 (68%) were men. SCS was present in 127/278 (46%) patients (70% in men) and in 164/556 (29%) neck sides. PRs revealed ipsilateral CACs in 138/164 (84%) neck sides with SCS. In total, CACs in PRs were observed in 473 of all 556 neck sides (85%). In Group A, 12/115 (7%) patients had SCS; all were found in men (12/112 (11%)) and men comprised 69% of the study population.

4.4.1 Neck side level – distribution of radiographic appearances

On neck side level all participants from Group A and B that presented CACs in PRs were included.

The radiographic appearance of CAC specified as vessel-outlining was observed in 65% (90/138) of neck sides with SCS compared to in 47% (157/335) of neck sides without SCS, ($p < 0.001$).

In men, the category specified as vessel-outlining was observed in 64% of neck sides with SCS and in 45% of neck sides without SCS. In women, the vessel-outlining specified category was found in 68% of neck sides with SCS and in 50% of neck sides without SCS, ($p = 0.93$).

The category specified as single CAC or a tight conglomerate of several CACs, was observed in 15% (21/138) of neck sides with SCS and in 27% (91/335) of neck sides without SCS, ($p = 0.006$).

The category specified as scattered was observed in 20% (27/138) of neck sides with SCS and in 26% (88/335) of neck sides without SCS, ($p = 0.127$).

The interobserver agreement regarding all specified categories of CACs in PRs (including neck sides with no CACs) showed a Kappa value of 0.68. The interobserver agreements regarding the vessel-outlining, single and scattered categories were 0.78, 0.61 and 0.53 respectively.

4.4.2 Patient level – combinations of radiographic appearances

In the analysis on patient level the 163 odontologically examined patients from Group A that presented CACs in PRs were included. The analysis was based on the results obtained in the analysis on neck side level regarding correspondens between radiographic appearance and likelihood for SCS. Patients with solely single specified CACs were included only in the analysis resembling the conventional method when considering all radiographic appearances of CACs.

Three subgroups, comprising patients with following combinations of specified CAC-categories, were studied regarding the possibility to improve PPV for SCS detection compared to the PPV obtained in the conventional method. Subgroups were defined as follows:

- (I)** patients with vessel-outlining CACs on any side
- (II)** patients with vessel-outlining CACs on any side and patients with bilateral scattered CACs
- (III)** all patients, except those with only single CACs (i.e. patients with vessel-outlining CACs on any side and patients with scattered CACs on any side).

In the different subgroups of Group A false positive findings were reduced by 25-37%. At the same time 17-33% of patients with SCS were missed. As a consequence the PPVs calculated for each of the three combinations were very similar to the PPV calculated for the conventional method. (Table 4)

Subgroups of CAC-categories	SCS (%)		PPV (95% CI)
	Yes	No	
I	8 (67%)	95 (63%)	7.8% (2.5-13.0%)
II	9 (75%)	111 (74%)	7.5% (2.7-12.3%)
III	10 (83%)	128 (85%)	7.2% (2.9-11.6%)
All	12 (100%)	151 (100%)	7.4% (3.3-11.4%)

Table 4. Frequencies of patients with carotid artery calcifications (CAC) in panoramic radiographs with or without significant carotid stenosis (SCS) in subgroups (I-III) and in all patients. Positive predictive values (PPV) for SCS detection and 95% CI are shown for each subgroup. **I.** Patients with *vessel-outlining CAC* on any side; **II.** Patients with *vessel-outlining CAC* on any side as well as patients with bilateral *scattered CACs*; **III.** Patients with *vessel-outlining CAC* on any side as well as patients with *scattered CACs* on any side; **All.** All patients presenting CAC, independent of radiographic appearance (conventional method)

The binomial test revealed no significant improvements of PPV compared to the conventional method ($p = 0.12$) or compared to subgroup I that had the highest PPV of all subgroups ($p = 0.14$).

5 Discussion

5.1 Main findings

Screening with carotid ultrasound for SCS is indicated in men, eligible for asymptomatic CEA, that present CACs in PRs (Study I). Individuals with CACs in PRs reveal a higher burden of atherosclerotic diseases compared to individuals without CACs in PRs (Study I). PRs disclose the majority of patients with SCS by means of CACs, and almost all of extirpated carotid plaques reveal calcification (Study II). Calcification volume within extirpated carotid plaque is not associated with degree of SCS, i.e. both small and large CACs depicted in PRs can represent neck sides with SCS (Study III). Radiographic appearances of CACs, as perceived in PRs, can be associated with SCS. However, the use of radiographic appearances as specified in this study does not increase PPV regarding SCS detection in an odontologically examined adult population < 75 years presenting CACs in PRs (Study IV).

5.2 Study design

All studies are performed with cross-sectional design.

5.2.1 Study population – Group A

The study population in Group A comprised patients between 18 and 74 years examined with PR. The population was prospectively and consecutively sampled and patients had to be of relative good health i.e. eligible for asymptomatic CEA. The inclusion rate was good since only few eligible patients were missed (5%).

In Study I, men and women were included at equal proportions and 80% of the included patients were examined for ordinary dental reasons. The population used in Study I is therefore considered representative for adult patients < 75 years examined in general dentistry that present CACs in PRs.

In part of Study IV the study population of Group A was increased, exclusively with men, due to altered clinical inclusion criteria following the results from Study I. The representative population from Study I was increased with these additional patients with the intention to create a study population containing a large proportion of odontologically examined patients presenting CACs in PRs.

5.2.2 Reference group

The age and gender matched reference group in Study I was randomly and retrospectively selected among all patients examined with PR that did not present CAC.

5.2.3 Study population – Group B

The study population in Group B comprised patients with SCS examined with PR and FR. The population was prospectively and consecutively sampled. In Study II and III the participants had also undergone CEA. The inclusion rate of patients in Study II and III was good; only 7% of eligible patients were missed. Study IV also included patients with SCS that were given medical treatment alone. They were examined with PRs and FRs because the initial treatment plan included CEA, but CEA was later cancelled due to e.g. technical CEA-difficulties or denial. In part of Study IV they were included with the intention to create a study population containing a large proportion of patients with SCS.

Both symptomatic and asymptomatic patients were included. CEA is performed in *symptomatic* patients with SCS of 50-99% and with acceptable perioperative risk. CEA is performed in *asymptomatic* patients < 75 years with SCS of 70-90% and low perioperative risk [40]. Among those that underwent CEA, 70% were men and 85% were symptomatic. They constitute a representative European CEA-population. Treatment with CEA in asymptomatic patients has differed over time and between different centres. For comparison, in the US more than 50% of all CEA are performed in asymptomatic patients. In the early '90s, when the results of the randomized asymptomatic CEA trials were published, the number of CEA almost tripled in the US and Canada [48, 93]. Improvements in the field of medical intervention may alter the criteria for surgical treatment among asymptomatic patients in future.

5.3 Methodology

PRs, FRs, carotid ultrasound and CT-angio examinations were all performed according to standard protocols.

The carotid ultrasound examinations were performed by experienced vascular sonographers and diagnosis assessment was locally validated [92]. Carotid ultrasound and CT-angio examinations generated the same result in 95% of the patients that had undergone both examinations.

All PRs and FRs were analysed by two experienced specialists in oral and maxillofacial radiology (JA, ELJ). High inter-observer Kappa values were calculated regarding identification of CACs in both PRs and FRs.

Presence or absence of calcification within extirpated carotid plaques was in agreement in both 3D-CBCT and 2D-radiographic examinations. CBCT-measurements were performed according to a specially designed protocol. Since CT-Hounsfield units cannot be transferred to CBCT-examinations, measures of calcification volumes should be considered as relative.

5.3.1 Validity

Inclusion criteria for the study populations, including examination protocols, were well defined. Study participants had a high inclusion rate and are considered as representative populations. The fact that all PRs and FRs were analysed by two specialists in oral and maxillofacial radiology strengthens internal validity but weakens to some extent external validity.

5.4 Comparisons and subgroup findings

5.4.1 Prevalence of carotid artery calcifications

Prevalence of CACs in PRs of participants in Study I was reported with higher prevalence compared to previous studies [71, 79]. There are several factors that to some part can explain the higher reported prevalence: (1) The PRs used in this thesis were digitally processed which gives the possibility to adjust contrast levels that can facilitate diagnosis in e.g. the area of the carotid arteries that sometimes is overexposed. (2) CACs are reported with higher frequency among elderly [73] and the study participants in Study I had a slightly higher mean age compared to one of the other comparable studies [79]. (3) The PRs were analysed for CACs by two experienced specialists in oral and maxillofacial radiology and patients with both small and large CACs in PRs were referred for carotid ultrasound examination. Small CACs can be difficult to differentiate from other calcified structures that appear within the same area in the PR and might have been missed in previous reported studies. (4) Pro-atherogenic risk factors differ between different geographic areas [94] which might affect prevalence of CACs in PRs.

5.4.2 Comparisons between study and reference group

Among the participants in Study I without SCS, carotid ultrasound revealed calcified nonstenotic carotid plaques in 99% of neck sides that presented CAC in PRs. Carotid plaques are sign of advanced atherosclerotic disease [53, 54].

Participants of the study group were more associated with cardiovascular risk factors and had to a higher degree experienced cardiovascular events compared to the participants in the reference group. The fact that the participants of the study group revealed a higher than average burden of atherosclerotic disease might also contribute to the higher prevalence of CACs observed in the PRs compared to previous reported studies.

5.4.3 Prevalence of carotid stenosis

In Study I SCS were reported with lower prevalence compared to previous studies [71, 79]. This difference can partly be explained by: (1) Differences in study design; previous studies have included patients > 75 years of age and most of them were men. Asymptomatic SCS occur with higher prevalence in men and individuals > 70 years [41, 42]. (2) The ultrasound threshold for SCS $\geq 50\%$ was lower in the study by Friedlander (peak systolic velocity 1.25 m/s in the internal carotid artery) [79] compared to the threshold used in Study I (peak systolic velocity 1.45 m/s in the internal carotid artery). The lower threshold almost doubled the prevalence of SCS in the study population of Study I [95]. The peak systolic velocity that defined the level for SCS $\geq 50\%$ was not specified in the study by Almog et al 2002 [71].

In Study I, prevalence of ultrasound verified SCS was statistically significant over the pre-specified threshold of 5% in men (all SCS were found in men). The patients with SCS and CACs in PRs were also more associated with atherosclerotic related cardiovascular events and risk factors compared to the patients with CACs in PRs without SCS. As already described in the introduction, treatment with CEA of individuals with asymptomatic SCS is heavily debated. The pre-specified 5%-threshold will most certainly be changed and the conclusions of Study I have to be revised thereafter.

5.4.4 Carotid calcifications in patients with SCS

All but one of the extirpated carotid plaques revealed calcification (Study II, III). PRs disclosed 75% of the calcifications on the neck side ipsilateral to the calcified extirpated carotid plaque (Study II). These findings are similar to a previous study with similar study design that included patients with SCS

≥ 70% [84]. In Study II, PRs disclosed 84% of patients with SCS by findings of CACs on the same or contralateral (9.5%) to the neck side with SCS.

The high frequency of calcification found within extirpated carotid plaques increases the possibility to depict patients with SCS in PRs. The results from Study III reveal that the amount of calcification within carotid plaques does not affect the possibility to detect CACs in PRs, since both the smallest and largest calcification quantities measured could be depicted. In fact, the main reason that calcified SCS were not seen in the PRs was that they were positioned below the region depicted by the PR (Study II). The amount of calcification within extirpated carotid plaques was not associated with the degree of SCS and did not differ between subgroups of gender, age and asymptomatic/symptomatic SCS (Study III). In conclusion, both small and large observed CACs in PRs can represent neck sides with SCS, independent of age, gender and type of SCS (Study III). To measure CAC quantities in PRs as done in a previous study [89] to test for correlation with degree of SCS is therefore inadvisable. In addition, measurements of the amount of CACs in PRs are not accurate given the functional principles behind the creation of a PR image and the relatively high probability that parts of the CAC are situated outside the region actually depicted by the PR. Moreover, PRs only reveal the calcification within atherosclerotic plaques. PRs do not reveal the soft tissues that surround the calcification which mainly lead to luminal reduction. The results from Study III have shown that the size of CAC in PRs cannot be used to improve the detection of individuals with SCS.

5.4.5 Radiographic appearance of carotid artery calcifications

Study IV aimed to reconnect to the results obtained in Study I where 7% of the patients with CACs in PRs had ultrasound verified SCS. This prevalence is comparable with PPVs. The purpose with Study IV was to improve the selection of patients towards higher PPVs regarding SCS detection by reducing the number of false positives i.e. patients with CACs in PRs but without SCS.

CACs in all participant neck sides, were in the analysis on neck side level categorized into three groups based on their radiographic appearance in PRs (single, scattered or vessel-outlining). The distribution of these specified categories was then analysed in neck sides with and without SCS in participants of Group A and B. The hypothesis was that neck sides with vessel-outlining CACs were more associated with SCS compared to categories specified as single or scattered.

According to the results from Study I, 99% of CACs observed in PRs are associated with a nonstenotic calcified carotid plaque i.e the calcifications

visible in PR are surrounded by a soft tissue mass not visible in PR. Vessel-outlining CACs were specified as two parallel and vertically aligned single or scattered CACs that give the impression of outlining the anterior and posterior contours of a vessel. The likelihood for luminal reduction should be higher in the case of two parallel-situated CACs observed in PRs compared to the other two defined categories since two parallel calcifications are likely associated with opposing atherosclerotic soft tissue masses. Neck sides with vessel-outlining CACs were significantly more associated with SCS compared to the other two specified categories and there were no differences between genders regarding that association. However, vessel-outlining CACs were also represented in almost half the number of neck sides without SCS.

Neck sides with single CACs were significantly less associated with SCS and neck sides with scattered CACs appeared in the same frequency in neck sides with and without SCS. Inter-observer Kappa values regarding all radiographic appearances were moderate.

Analysis on patient level was solely performed in patients of Group A since they represent an odontologically examined adult population < 75 years. Three subgroups derived from the specified CAC-categories were analysed. All three subgroups yielded PPVs for SCS detection similar to the conventional method where any presence of CACs in PRs was considered. The number of false positives was reduced by 25-37% in the various subgroups but at the same time 17-33% of patients with SCS were missed. The results imply that there is no advantage or practicable use in categorizing CACs in PRs according to the definitions used in Study IV. Whether the different radiographic appearances of CACs in PRs are associated with future risk of stroke and other cardiovascular events remain unknown.

5.5 Considerations and limitations

Women and men were included with equal proportions in Study I; however, none of the women with CACs in PRs revealed SCS. Women have a lower prevalence of asymptomatic SCS compared to men [41, 42] but women and men with SCS reveal CACs in PRs at equal proportions (Study II) and calcification quantity within extirpated calcified SCS do not differ between genders (Study III). The result of significant gender difference in Study I might be false positive (type I error). A larger sample size than that used in Study I is required to answer the question whether screening for SCS with carotid ultrasound is indicated also in women presenting CACs in PRs.

It remains unknown if the outcome of PPV in any of the three different used subgroups in Study IV would have been different if women with SCSs had been present in Group A.

None of the participants in the reference group in Study I were examined with carotid ultrasound since they did not present CACs in the PRs. It is possible that some participants within this group had asymptomatic SCS. However, this possibility is considered rather small, since the majority of individuals with SCS reveal CACs in PRs (Study II).

According to the results from Study II, 12% of patients with SCS were missed due to the requirement that a CAC had to be identifiable in both the PR and the FR. The results from Study II therefore imply that the use of FRs do not contribute to the identification of individuals with SCS but, on the contrary, can reduce the possibility to identify individuals with SCS.

In Study III calcification quantities were measured in, and restricted to, extirpated carotid plaques. It cannot be guaranteed that the observed CAC in the PR corresponds to the calcification observed in the extirpated carotid plaque because small remnants of atherosclerotic calcification could remain after CEA. Further, the results obtained in Study III are restricted to patients (and extirpated carotid plaques) with SCS $\geq 50\%$. Whether calcification quantities differ among patients with nonstenotic carotid plaques remains unknown.

Study II and III included few asymptomatic participants. The results from the subgroup analysis for the asymptomatic patients should therefore be interpreted with caution.

The members of the Regional Ethical Board in Umeå were concerned about how patients examined for odontological reasons would accept the information, provided by a dentist, regarding the potential risk of having a SCS with increased risk for stroke due to findings of CACs in PRs. The patients with CACs were given both oral and written information and the overall majority of patients responded positively to the referral for carotid ultrasound examination.

5.6 Perspectives

As previously stated, SCS are risk markers for future vascular events (i.e. cerebrovascular disease (stroke/TIA), cardiovascular disease, claudication, arterial revascularization and vascular death) and individuals with asymptomatic SCS warrant intensive medical intervention [51, 53-55, 96, 97]. To date it is unknown whether individuals with nonstenotic carotid plaques benefit from intensive medical therapy; however, benefit from

therapy seems reasonable since this subgroup has an increased risk of combined vascular events in comparison to individuals without carotid plaques [57].

In Study I, the participants of the study group (with CACs in PRs) were more associated with cardiovascular risk factors and had to a higher degree experienced previous cardiovascular events compared to the participants of the reference group (without CACs in PRs). This implies that individuals, independent of gender, with findings of CACs in PRs are at risk for future cardiovascular event.

The study and reference group in Study I have been followed for 5.4 years [98]. During that time, participants from the study group revealed a 5.6% increased risk to reach a combined vascular event compared to 2.4% for the participants in the reference group, ($p = 0.004$). However, this increased risk was no longer statistically significant when previous vascular risk factors and events were considered. The conclusions from that study were that individuals with CACs in PRs have a higher prevalence of vascular risk factors and an increased risk of future vascular events compared to individuals without CACs in PRs. Individuals with CACs in PRs should therefore be advised to have their vascular risk factors checked, especially if they never have had a thorough examination of vascular risk factors [98].

Future studies will reveal if individuals with nonstenotic carotid plaques will benefit from intensive medical intervention. If intensive medical intervention is proven beneficial in individuals with nonstenotic carotid plaques, patients with incidental findings of CACs in PRs, independent of age and gender, should be included in prevention and care programs.

5.7 Conclusions

SCS are found in 7% of patients (12% in men) that reveal incidental findings of CACs in PRs performed for odontological reasons. Screening with carotid ultrasound for SCS is indicated in men eligible for asymptomatic CEA that present CACs in PRs. Patients with CACs in PRs are more associated with cardiovascular risk factors and have to a greater extent experienced previous cardiovascular events than patients without CACs in PRs. Patients without previous record of cardiovascular disease and with CACs in PRs, independent of size and appearance, should be advised to seek medical attention for screening of cardiovascular risk factors. Almost all CACs in PRs correspond to a calcified atherosclerotic carotid plaque according to carotid ultrasound examination.

The majority of extirpated carotid plaques are calcified and three out of four are identified in PRs by means of ipsilateral CACs. The majority of patients with SCS reveal CACs in PRs, sometimes contralateral to the neck side with SCS. The most common reason for calcified carotid plaques not being detected in PRs is that they are positioned below the depicted region.

Calcium volume in extirpated carotid plaques is not associated with degree of SCS, i.e. both large and small CACs in PRs can represent neck sides with SCS. Calcium volume does not influence the possibility to detect CACs in PRs; as long as the calcium volume is $\geq 1 \text{ mm}^3$.

The radiographic appearance of CACs in PRs can be associated with SCS. However, the use of radiographic appearances, as specified in this study, does not improve PPV for SCS detection compared to when only considering presence of CACs.

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