

# Early Diagnosis and Treatment of Coronary Heart Disease in Asymptomatic Subjects With Advanced Vascular Atherosclerosis of the Carotid Artery (Type III and IV b Findings Using Ultrasound) and Risk Factors

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## Abstract

**Background:** A study was conducted as to whether the early diagnosis of coronary heart disease in asymptomatic subjects with advanced atherosclerosis of the carotid artery which additionally shows at least one risk factor is successful using ultrasound technology.

**Methods:** Within the scope of an occupational screening program using subjects from diverse employment sectors, people were given the opportunity to determine their risk of heart attack. During the study the total plaque area (TPA), the maximum plaque thickness in the carotid artery and the PROCAM-Scores of 3,748 healthy men and 2,260 healthy women between the ages of 20 and 64 years were determined. During the subsequent follow-up study 94 subjects sickened. An ultrasound examination of the carotid artery of 79 patients revealed a type III or IV b finding. In a pilot study 33 asymptomatic subjects with a type III or IV b finding in the ultrasound examination were assessed using a computed tomography (CT) coronary angiogram. Additional 10 asymptomatic subjects were examined independently to undergo further cardiac examinations.

**Results:** In the final analysis only five patients had entirely smooth coronary arteries, six had coronary sclerosis, eight had a 30% stenosis, one had a 30-50% stenosis and 23 patients had a stenosis  $\geq$  50%; and in extreme case, a left main coronary artery stenosis with three-vessel disease.

**Conclusions:** Asymptomatic subjects with advanced atherosclerosis of the carotid artery (type III and type IV b findings) had a high risk for coronary heart disease (CHD). Early treatment of the disease improves the patient's prognosis. A screening consisting in the combi-

nation of TPA measurement and determining the maximum plaque thickness is recommended.

**Keywords:** Total plaque area; Carotid ultrasound; Cardiovascular risk; Coronary heart disease; PROCAM-score

## Introduction

Within the scope of an occupational screening program in the Koblenz area people working in diverse sectors of the economy such as chemicals, glass, pharmaceuticals, administration, steel production, social services, paper production, printing, ceramics, IT, university, universities of applied science and retail were given the opportunity to determine their risk of heart attack. During the study the total plaque area (TPA), the maximum plaque thickness in the carotid artery and the PROCAM-Scores of 6,008 healthy subjects (who had had no previous history of a cardiovascular event) between the ages of 20 and 64 years (3,748 men and 2,260 women) were determined.

In the mean follow-up study of period of  $47.3 \pm 23$  months, eight strokes and 31 heart attacks have occurred to date. A total of 10 bypass operations and nine stent implantations have been performed, and stenoses (30% - 100% respectively) have been revealed in seven patients who underwent a coronary angiogram. Five subjects exhibited a type III finding and 45 subjects a type IV b finding in the ultrasound examination of the baseline study.

The testing method involving the measurement of plaque burden and maximum plaque thickness was validated by means of a blinded examination of 500 patients in hospital 1 day prior to a scheduled coronary angiogram. This allowed the classification of the ultrasound findings into four types [1]. Study of the patients with a type III or a type IV b finding in the ultrasound examination revealed one, two or three-vessel disease in 83% of the cases. Totally 87% of the patients suffering from a stenosing coronary heart condition were accurately predicted (type III or type IV b finding during the carotid duplex).

Subsequently, 464 healthy subjects (84 of them women) with a type III or type IV b finding were contacted and specifically asked if they had experienced, or were experiencing symptoms such as exertional dyspnea or angina pectoris. To-

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tally 39 subjects (32 men and 7 women aged between 43 and 61 years) complained of exertional dyspnea or of atypical angina pectoris or typical angina pectoris. In the case of all subjects there was advanced atherosclerosis of the carotid artery (type III or type IV b finding), and further cardiac assessment was recommended.

In the final analysis three patients had entirely smooth coronary arteries, seven had coronary sclerosis, eight had a 30-40%, and 21 patients had a stenosis  $\geq 50\%$ . A stent was inserted into seven of these patients and two patients underwent emergency bypass surgery following a coronary angiogram (both patients had main stem stenosis, three-vessel disease) [2].

In a pilot study 33 asymptomatic subjects with a type III or IV b finding in the ultrasound examination and with at minimum one risk factor (LDL-cholesterol  $\geq 180$  mg/dL, HDL-cholesterin  $\leq 40$  mg/dL, positive family history) were assessed using a computed tomography (CT) coronary angiogram. Additional 10 asymptomatic subjects were examined independently to undergo further cardiac examinations.

## Methods

The carotid artery (common carotid artery both externally and internally using B-mode ultrasound) was examined on both sides, as far as could be made visible, for plaques on the long and short axis from the clavicle through to the temporomandibular joint in a caudal to cranial direction by means of anterior, anterolateral, lateral and posterolateral insonation. A portable ultrasound device with a 10 MHz linear transducer of the type Imagic Agile and manufactured by the company Kontron Medical was used during testing. Only carotid artery wall thickness increases with an intima media thickness (IMT)  $> 1$ mm were evaluated as plaque. Using the device's surface area measurement program it was possible to identify all the plaques in a longitudinal section (the sum total of all plaque surface areas TPA) by tracing the perimeter of each plaque with the cursor at its maximum enlargement in the B-mode image. Furthermore, the maximum plaque thickness was measured. The findings of the ultrasound examinations were classified according to four types ranging from type I to type IV b [1].

Type I: no or only minimal atherosclerosis of the carotid artery with a TPA of up to 24 mm<sup>2</sup>; Type II a: only flat plaques  $\leq 2$ mm IMT with plaque surface area  $<$  age-related cut-off in the carotid artery; Type II b: only flat plaques  $\leq 2$ mm IMT with a large plaque surface area above age-related cut-off in the carotid artery; Type III: carotid plaques with an IMT  $\geq 3.5$  mm and a plaque surface area  $<$  age-related cut-off; Type IV (mixed type): a) with flat carotid plaques and plaques  $> 2$  mm IMT and a plaque surface area  $<$  age-related cut-off, b) with flat carotid plaques and plaques  $> 2$ mm IMT and a large plaque surface area over age-related cut-off.

The TPA cut-off in the case of subjects  $< 40$  years of age is 60 mm<sup>2</sup>, from 40 to 49 years of age is 80 mm<sup>2</sup>, from 50 to 59 years of age is 110 mm<sup>2</sup>, and from 60 to 64 years of age is 130 mm<sup>2</sup>. The cut-off for maximum plaque thickness is  $> 2$  mm, or irrespective of the TPA is  $\geq 3.5$  mm.

According to this classification it was possible to predict

coronary stenosis in patients who were examined one day prior to their undergoing a coronary angiogram with a sensitivity level of 87% [1].

Totally 40 subjects were assessed using a CT coronary angiogram (80 row MS-CT Toshiba Aquillon Prime) with native scan and bolus triggered contrast media and in three subjects directly using coronary angiograms because of pathological exercise ECG or dysrhythmia.

The study was approved by the responsible Ethics Committee and Federal Office for Radiation Protection.

## Results

The initial cardiac diagnostic testing was conducted on 40 subjects using a CT coronary angiogram and three subjects were assessed using coronary angiogram.

An ultrasound examination of the carotid artery of 40 patients revealed a type IV b finding, and in three subjects the examination revealed a type III finding.

In the final analysis five subjects had entirely smooth coronary arteries, six had coronary sclerosis, eight had a 30% stenosis, one patient had a 30-50% stenosis and 23 patients had a stenosis  $\geq 50\%$ . A stent was inserted into five of these patients and two patients underwent emergency bypass surgery following a coronary angiogram (both patients had main stem stenosis, three-vessel disease)

Table 1 gives an overview of the clinical data. Table 2 gives an overview of the baseline-data of the assessed subjects.

## Discussion

Atherosclerosis is an inflammatory disease of the arteries and continues to be the most common cause of death (40%) in the developed industrial nations. The disease can even begin from the age of 20 years and often remains undetected until it is in its later stages, resulting in clinical events such as acute coronary syndrome, stable angina, apoplexy and peripheral artery disease (PAD). Several studies demonstrate that even insignificant coronary stenoses are associated with an increased risk of heart attack [3-5]. An extensive multicenter research study (CONFIRM-Study) using 27,000 CT coronary angiograms revealed that statin therapy contributes towards an improvement in survival chances even in the case of stenoses  $< 50\%$  [6]. The improvement in survival chances achieved by using statin therapy in the group of subjects with non-obstructive coronary heart disease (CHD) was at a hazard ratio of 0.39; 95% confidence interval (CI) (0.23 - 0.65);  $P < 0.001$ . This effect was not verifiable in the group with normal coronary arteries. It therefore appears important that atherosclerosis is both diagnosed and treated in its early stages in order to delay the final outcome of the disease as long into the future as is possible. Several studies revealed that statin therapy contributes towards an improvement in survival chances in primary prevention [7-9] and that that subjects with advanced carotid atherosclerosis have significantly increased risk for heart attack and stroke [10-25].

**Table 1.** Test Results of the 43 Asymptomatic Subjects With a Type III or IV b Finding in the Ultrasound Examination

Sex	Age	PRO-CAM	TPA	Plaque thickness	Type ultrasound	Symptoms	Risk factors	Diagnostics	Coronary result	Therapy	Exercise ECG
M	58	15.20%	199	2.7	IV b	none	LDL,	exercise-ECG, Coro	smooth vessels	conservative	negative
W	57	6.53%	135	2.6	IV b	none	LDL, FA	CT	smooth vessels	conservative	
M	37	0.78%	65	2.3	IV b	none	LDL	CT	smooth vessels	conservative	
M	47	13.66%	182	2.8	IV b	none	LDL	CT	smooth vessels	conservative	
M	56	27.50%	128	2.7	IV b	none	HDL, FA	CT	smooth vessels	conservative	
M	48	21.54%	156	2.6	IV b	none	LDL, FA	CT	sclerosis	conservative	
M	59	30.80%	182	2.9	IV b	none	LDL, HDL, FA	CT	sclerosis	conservative	
M	53	13.44%	119	2.3	IV b	none	HDL, FA	CT	sclerosis	conservative	
W	57	7.00%	94	3.8	III	none	LDL, FA	CT	sclerosis	conservative	
M	54	19.96%	217	3.2	IV b	none	HDL, FA	CT	sclerosis	conservative	
W	57	2.17%	171	3.0	IV b	none	LDL, FA	CT	sclerosis	conservative	
M	60	28.43%	135	3.4	IV b	none	LDL	CT	30% HS	conservative	
M	49	24.59%	80	2.1	IV b	none	LDL, FA	CT	30% LAD	conservative	
W	56	4.07%	128	4.2	IV b	none	LDL, FA	CT	30% LAD	conservative	
W	59	4.94%	159	3.2	IV b	none	LDL	CT	30% LAD, RCX	conservative	
W	61	33.21%	177	2.8	IV b	none	LDL, FA	CT	30% LAD, RCX	conservative	
M	59	10.53%	218	3.6	IV b	none	HDL, FA	CT	30% LAD, RCX	conservative	
M	46	3.90%	106	4.1	IV b	none	LDL	CT	30% RCA	conservative	
M	52	4.00%	128	3.5	IV b	none	FA	exercise-ECG, CT	30% LAD	conservative	negative
M	49	11.62%	127	4.5	IV b	none	HDL, FA	CT	30-50% RCX	conservative	
M	58	30.44%	332	3.3	IV b	none	HDL, FA	CT	50% LAD	conservative	
M	53	24.67%	159	3.0	IV b	none	LDL	CT	50% RCA	conservative	
M	62	35.60%	131	2.3	IV b	none	LDL	CT	50% RCA, RCX	conservative	
M	47	3.04%	90	2.1	IV b	none	LDL,	Coro	50% RCX	conservative	
W	58	36.90%	185	2.4	IV b	none	LDL, DM, FA	exercise-ECG, CT	50% LAD	conservative	negative
M	53	7.55%	193	3.5	IV b	none	LDL	CT	50% RCA, LAD	conservative	
M	58	5.12%	137	2.5	IV b	none	none	CT	50% LAD, RCA	conservative	
M	64	16.92%	164	3.6	IV b	none	HDL, FA	CT, Coro	50-70% 3GE	conservative	
M	61	19.49%	156	4.6	IV b	none	HDL, FA	CT	60-70% LAD	conservative	
M	44	15.82%	122	2.3	IV b	none	LDL, HDL	exercise-ECG, CT, Coro	60-70% LAD, RCX	conservative	negative
M	55	5.88%	91	3.8	III	none	FA	exercise-ECG, CT, Coro	70% LAD	conservative	negative
M	62	38.96%	145	3.7	IV b	none	HDL	CT, Coro	70% LAD, RCA	conservative	
M	59	29.73%	148	3.3	IV b	none	HDL, FA	CT	70-90% LAD	conservative	
W	46	3.11%	54	3.5	III	none	LDL	exercise-ECG, CT, Coro	75% RCX, 60% LAD	conservative	negative
M	60	36.37%	172	3.5	IV b	none	LDL	CT, Coro	90% RCX	conservative	
M	52	6.04%	228	3.1	IV b	none	HDL, FA	CT	70-80% LAD, RCA	conservative	
M	63	3.95%	131	2.2	IV b	none	none	exercise-ECG, CT, coro	70-80% LAD, 3 GE	stenting	pathological
M	57	26.55%	165	2.3	IV b	none	LDL, FA	CT, Coro	70% LAD	stenting	pathological
M	56	37.51%	110	2.8	IV b	none	HDL, FA	CT, Coro	70-90% RCA, LAD	stenting	
M	61	23.07%	255	3.7	IV b	none	LDL	CT, Coro	90% 3 GE	stenting	negative
M	52	16.37%	210	4.0	IV b	none	LDL, HDL	CT, Coro	100% RCA, 3 GE	stenting	
M	63	14.66%	221	2.5	IV b	none	HDL, FA	Coro	80% HS, 3-GE	bypass	pathological
M	49	23.29%	138	3.1	IV b	none	LDL, HDL	CT, Coro	100% RCX, RCA, 3-GE, HS	bypass	

**Table 2.** Baseline Characteristics of All Subjects Between the Ages of 35 to 64 Years

Characteristics	Male without type III, IV b n = 2,688	Male with type III, IV b n = 382	Female without type III, IV b n = 1,898	Female with type III, IV b n = 82
Age	48 ± 7	54 ± 6	49 ± 7	54 ± 5
BMI, weight	27.33 ± 3.97	27.96 ± 4.20	25.25 ± 4.79	25.07 ± 4.19
Smoker	610 (22.7%)	165 (43.2%)	383 (20.2%)	38 (46.3%)
LDL-cholesterol	150 ± 34	158 ± 39	141 ± 33	161 ± 39
HDL-cholesterol	51 ± 12	48 ± 11	65 ± 15	62 ± 14
Triglyceride	170 ± 121	190 ± 120	109 ± 58	136 ± 71
Systolic blood pressure	127 ± 15	135 ± 18	121 ± 17	130 ± 19
Diastolic blood pressure	81 ± 8	84 ± 9	78 ± 9	79 ± 12
Diabetes	91 (3.4%)	32 (8.4%)	28 (1.5%)	5 (6.1%)
Treated blood pressure	514 (19.1%)	139 (36.4%)	313 (16.5%)	34 (41.5%)
Positive family history	573 (21.3%)	108 (28.3%)	521 (27.4%)	33 (40.2%)
Total plaque area (TPA mm <sup>2</sup> )	30 ± 34	150 ± 63	17 ± 24	120 ± 62
Max plaque thickness (mm)	1.7 ± 0.5	3.0 ± 0.8	1.6 ± 0.5	3.2 ± 0.6
PROCAM-risk	6.02% ± 6.74%	13.32% ± 10.29%	1.35% ± 2.4%	4.81% ± 6.63%
Sick (≥ 30% stenosis, infarction etc).	13 (0.5%)	98 (25.6%)	2 (0.1%)	12 (14.6%)

In total, 382 of the examined men and 82 of the examined women showed this finding. In the follow-up study it was found that 49% of the men and 33% of the women who were examined with ultrasound between 2009 and 2011 and showed a type III or type IV b finding were already diseased.

In total, 23.7% of the men and women with a type III or IV b finding are diseased (e.g. apoplex, infarction, bypass-operation, stent, coronary stenosis ≥ 30%). In the baseline examination with ultrasound 80% of the 65 diseased men and women in the follow-up showed a type III or IV b finding. Overall, 10% of the 82 subjects (39 symptomatic, 43 asymptomatic) who were examined with a cardiac CT or a coronary angiography showed smooth vessels, 74% showed a coronary stenosis of 30-100% and 53% a stenosis ≥ 50%. The correlation between atherosclerosis of the carotid artery and the coronary vessels in the case of asymptomatic subjects has been studied many times with the result that the positive predictive value (PPV) for CHD was significantly lower [26-30]. A possible reason for this result could be that the plaque burden of the carotid artery has not been quantified. For the 82 subjects the PPV for a coronary stenosis ≥ 30% is 0.74; (95% CI: 0.64 - 0.83). Interestingly, the results for the symptomatic and asymptomatic cohort are almost identical. Measuring plaque burden of carotid artery with quantification of the TPA and the maximal plaque thickness is a cost-effective, non-invasive screening tool without side effects which can be used to diagnose and to treat CHD in an early stadium. Assuming a prevalence of CHD of 5.5% for healthy men aged between 35 and 64 years and a sensitivity of the examination method of 80% for diagnosing coronary stenosis one finds the negative predictive value (NPV) to be 99% for the case of no type III or IV b finding. The actual results justify a therapy with statins for asymptomatic men and women with advanced atherosclerosis of the carotid artery. Though this kind of therapy is recommended in the current guidelines

in the case of diagnosed plaques, there is no exact quantification of the total amount of plaque burden [31]. Because 96% of the men aged between 60 and 64 years show plaques in the carotid artery, a therapy with statins would certainly lead to an overtreatment.

The limitation of this research is that only a small number of asymptomatic subjects were examined.

## Conclusions

Asymptomatic subjects with advanced atherosclerosis of the carotid artery (type III or type IV b finding) have a high risk of CHD and should be treated with statins.

TPA and plaque thickness measurement using ultrasound is a low-cost and simple screening method, and advisable for everyone over the age of 35 years.

## Conflict of Interest

The authors confirm that they have no conflict of interest.

## Abbreviations

TPA: total plaque area; FA: Family history positive; DM: Diabetes mellitus; HDL: HDL-cholesterol ≤ 40 mg/dL; LDL: LDL-cholesterol ≥ 180 mg/dL; AP: Angina pectoris; Coro: Coronary angiogram; CT: Computer tomography; HS: Left main; RF: Risk factor; Nik: Nicotine use; KHK: Coronary artery disease; PTP: Pre-test probability; GE: Vascular disease; ACS: Acute coronary syndrome

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