

The Determination of the Plaque Burden on the Carotid Artery With Ultrasound Significantly Improves the Risk Prediction in Middle-Aged Subjects Compared to PROCAM: An Outcome Study

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Abstract

Background: There are only few data about the predictive value of atherosclerosis imaging beyond traditional risk calculators in younger subjects.

Methods: We assessed cardiovascular risk prediction with the PROCAM (the Prospective Cardiovascular Munster Study) risk equation and with carotid plaque imaging (determination of total plaque area (TPA) and the maximum plaque thickness with ultrasound) in subjects without known cardiovascular diseases. The follow-up was generated during follow-up examinations as part of preventive medical examinations or by telephone calls.

Results: In 2,508 subjects aged 35 - 64 years (50 ± 8 years, 34% women), 132 (5.3%) cardiovascular events occurred (42 myocardial infarction, 17 bypass surgery, 31 stent implantation, 42 coronary artery disease defined by invasive angiography) during a mean follow-up period of 5.4 (1 - 12) years. TPA in combination with the maximum plaque thickness (type III - IV b plaques) tended to be superior compared to TPA, and both plaque imaging methods were superior to PROCAM: area under the curve (AUC) 0.9 (95% confidence interval (CI): 0.91 - 0.89) vs. 0.89 (95% CI: 0.90 - 0.88), $P = 0.2$ vs. 0.82 (95% CI: 0.84 - 0.81), $P = 0.001$; positive predictive value (PPV) 27% (95% CI: 0.31 - 0.22) vs. 19% (95% CI: 0.22 - 0.16) vs. 19% (95% CI: 0.27 - 0.13).

Conclusions: Amount of carotid plaque assessed by carotid plaque imaging significantly improves cardiovascular risk prediction beyond the PROCAM risk equation.

Keywords: Total plaque area; Carotid ultrasound; Cardiovascular risk; Coronary disease

Introduction

It was examined how well coronary artery disease (CAD) can be predicted by an ultrasound examination of the carotid artery. For this purpose, the sum of all plaque areas (total plaque area (TPA) and the maximum plaque thickness were determined. The prediction quality was compared to that of the PROCAM (the Prospective Cardiovascular Munster Study) score.

Previous studies have shown that advanced atherosclerosis of the carotid artery is associated with an increased risk of cardiovascular diseases [1-16]. An outcome study that works with age-dependent cut-off values for the plaque area combined with the maximum plaque thickness is new.

Materials and Methods

In 2,386 healthy men and 1,423 healthy women aged 35 - 64 years, the sum of all plaque areas (TPA), the maximum plaque thickness and the PROCAM risk were determined. A portable ultrasound device from Kontron Medical, Type Imagic Agile, with a 10 MHz linear transducer was used. The measurement method was carried out as previously published study [17, 18]: a low risk corresponds to a type I and type IIa finding on ultrasound, an intermediate risk to a type IIb and IVa finding, and a high risk to a type III and IVb finding. The PROCAM risk was calculated using the published calculator of the Assmann Foundation [19].

All studies were evaluated with the approval of the responsible ethics committee.

Results

A follow-up is available for 2,508 (65.8%) subjects. In these subjects (50 ± 8 years, 34% women) 132 (5.3%) cardiovas-

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cular events occurred (42 myocardial infarctions, 17 bypass surgery, 31 stent implantations, 42 coronary artery diseases defined by invasive angiography) during a mean follow-up time of 5.4 (1 - 12) years.

Analysis for the follow-up of 2,508 healthy men and women

In the receiver operating characteristic (ROC) analysis to predict cardiovascular events, the area under the curve (AUC) for type III and IVb was 0.9 (95% confidence interval (CI): 0.91 - 0.89) vs. 0.89 (95% CI: 0.90 - 0.88; $P = 0.20$) for the TPA without considering the plaque thickness vs. 0.82 (95% CI: 0.84 - 0.81; $P = 0.001$) for PROCAM (Fig. 1).

The four-field table showed a sensitivity of 85% (95% CI: 0.90 - 0.78) and a specificity of 87% (95% CI: 0.88 - 0.86), a positive predictive value (PPV) of 27% (95% CI: 0.31 - 0.22) and a negative predictive value (NPV) of 99% (95% CI: 0.99 - 0.99) with a prevalence of 5%.

For the TPA with a cut-off from 80 mm² (TPA 80), the sensitivity was 84% (95% CI: 0.90 - 0.77), the specificity 80% (95% CI: 0.82 - 0.78), the PPV 19% (95% CI: 0.22 - 0.16) and the NPV 99% (95% CI: 0.99 - 0.98) and for the PROCAM score a sensitivity of 21% (95% CI: 0.29 - 0.15), a specificity of 95% (95% CI: 0.96 - 0.94), a PPV of 19% (95% CI: 0.27 - 0.13) and a NPV of 96% (95% CI: 0.96 - 0.95) (Table 1).

In patients with a cardiovascular event, 11 (8.3%) of 132 patients had a low risk on ultrasound, nine (6.8%) had an intermediate risk, and 112 (84.9%) a high risk (definition of ultrasound risk see Fig. 2).

According to PROCAM, 57 (43.2%) of the 132 patients had a low < 10% risk, 47 (35.6%) an intermediate 10-19% risk and 28 (21.2%) a high $\geq 20\%$ risk (Fig. 2).

In addition to the outcome data, coronary angiography results were available in 297 subjects.

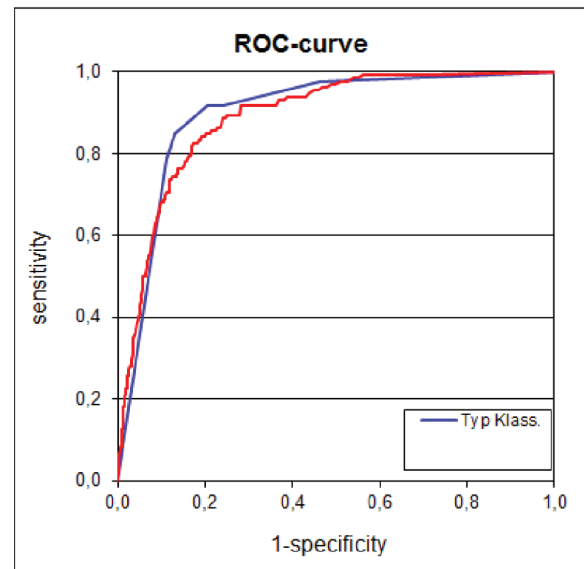
For these, the four-field table for the prediction of CAD showed a sensitivity of 85% (95% CI: 0.90 - 0.78) in ultrasound vs. 84% (95% CI: 0.90 - 0.77) in TPA 80 vs. 21% (95% CI: 0.29 - 0.15) in PROCAM; a specificity of 62% (95% CI: 0.70 - 0.55) vs. 48% (95% CI: 0.56 - 0.41) vs. 84% (95% CI: 0.89 - 0.77); a PPV of 64% (95% CI: 0.71 - 0.57) vs. 57% (95% CI: 0.64 - 0.49) vs. 51% (95% CI: 0.65 - 0.37); and a NPV of 84% (95% CI: 0.90 - 0.76) vs. 79% (95% CI: 0.87 - 0.70) vs. 57% (95% CI: 0.63 - 0.51).

With a cut-off for a coronary stenosis $\geq 30\%$, the sensitivity for the ultrasound resulted in 86% (95% CI: 0.91 - 0.80), a specificity of 71% (95% CI: 0.78 - 0.63), a PPV of 76% (95% CI: 0.82 - 0.69), and a NPV of 83% (95% CI: 0.89 - 0.75).

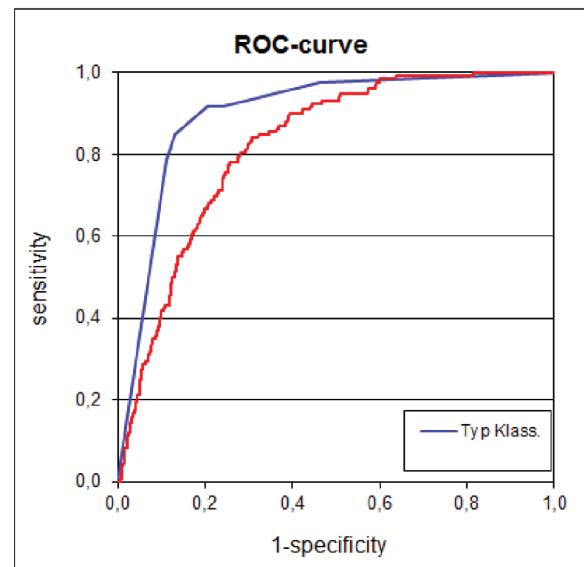
With type III or IVb findings on ultrasound (high risk), only 12% had smooth vessels, 23.6% had sclerosis to 40% stenosis and 64.4% had CAD (Fig. 3).

Discussion

Atherosclerosis is an inflammatory disease of the arteries and continues to be a major cause for morbidity and mortality in the industrialized nations. Fatty streaks can be found in arteries



| ROC CURVE | Typ Klass. | Tot Plaque are Diff. | |
|--------------|------------|----------------------|----------|
| AUC | 0.899 | 0.890 | 0.0090 |
| SE | 0.018 | 0.019 | 0.0071 |
| 0.95 low. CL | 0.887 | 0.877 | -0.0049 |
| 0.95 upp. CL | 0.911 | 0.902 | 0.0229 |
| COMPARISON | | | p 0.2034 |



| ROC CURVE | Typ Klass. | PROCAM-Risik | Diff. |
|--------------|------------|--------------|----------|
| AUC | 0.899 | 0.822 | 0.0771 |
| SE | 0.018 | 0.023 | 0.0161 |
| 0.95 low. CL | 0.887 | 0.807 | 0.0456 |
| 0.95 upp. CL | 0.911 | 0.837 | 0.1086 |
| COMPARISON | | | p 0.0000 |

Figure 1. Receiver operating characteristic (ROC) comparison of types I - IVb vs. TPA vs. PROCAM. TPA: total plaque area (carotid plaque); PROCAM: the Prospective Cardiovascular Munster Study.

already at the age of 20 years, and progression of atherosclerosis often remains undetected until clinical events such as acute coronary syndrome (ACS), chronic coronary syndrome (CCS),

Table 1. Four-Field Table for the Prediction of a Coronary Stenosis for TPA/Maximum Plaque Thickness vs. TPA 80 vs. PROCAM

| Test | CHD | | Total |
|------------------------------|-------------------------|-----|-------|
| | D- | D+ | |
| TPA/maximum plaque thickness | | | |
| T- | 2,066 | 20 | 2,086 |
| T+ | 310 | 112 | 422 |
| Total | 2,376 | 132 | 2,508 |
| SE | 85% (95% CI: 78% - 90%) | | |
| SP | 87% (95% CI: 86% - 88%) | | |
| PPV | 27% (95% CI: 22% - 31%) | | |
| NPV | 99% (95% CI: 99% - 99%) | | |
| Prev | 5% (95% CI: 4% - 6%) | | |
| TPA 80 | | | |
| T- | 1,904 | 21 | 1,925 |
| T+ | 472 | 111 | 583 |
| Total | 2,376 | 132 | 2,508 |
| SE | 84% (95% CI: 77% - 90%) | | |
| SP | 80% (95% CI: 78% - 82%) | | |
| PPV | 19% (95% CI: 16% - 22%) | | |
| NPV | 99% (95% CI: 98% - 99%) | | |
| Prev | 5% (95% CI: 4% - 6%) | | |
| PROCAM | | | |
| T- | 2,260 | 104 | 2,364 |
| T+ | 116 | 28 | 144 |
| Total | 2,376 | 132 | 2,508 |
| SE | 21% (95% CI: 15% - 29%) | | |
| SP | 95% (95% CI: 94% - 96%) | | |
| PPV | 19% (95% CI: 13% - 27%) | | |
| NPV | 96% (95% CI: 95% - 96%) | | |
| Prev | 5% (95% CI: 4% - 6%) | | |

TPA: total plaque area (carotid plaque); CHD: coronary heart disease; PROCAM: the Prospective Cardiovascular Munster Study; CI: confidence interval; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; Prev: prevalence.

apoplexy, and peripheral artery disease (PAD) occur.

In order to assess the quality of a diagnosis, the sensitivity and specificity or the results of the ROC analysis are usually given in studies. These values are not dependent on the prevalence of the disease, and can therefore show good results, although the PPV is low [20]. The lower the prevalence of the disease is, the higher the false positive rate with a low PPV. The opposite applies to the NPV. Screening inevitably produces a more or less high rate of false positive results and can therefore lead to overdiagnosis and therapy [21, 22]. During screening, the PPV and NPV are of particular importance for the subject to interpret the results. Measurement of TPA shows good data in the ROC analysis and for sensitivity and specificity with a cut-off of 80 mm², but at the expense of a significantly increased rate of false positive results with low PPV. A TPA of 80 mm² is alarmingly high for 35 - 49 year old,

but average for 55 - 64 year old [23]. Like many other risk scores, the PROCAM score is based only on the consideration of traditional risk factors such as age, gender, blood pressure, lipid values, smoking status etc., without taking into account the extent of atherosclerosis, which means that only 21% of those with a high risk were classified. Just like for the TPA method not taking into account the age-related plaque area and the maximum plaque thickness, the PPV with 19% is very low. The use of the PROCAM score means that the majority of those affected would not be treated with a statin. With a TPA 80 method, a large part of the sufferers are treated, but also many test subjects do not need statin. The best results (sensitivity 85%, PPV 27%) for the prediction of CAD are achieved if the extent of atherosclerosis in relation to age and the maximum plaque thickness are determined for risk stratification.

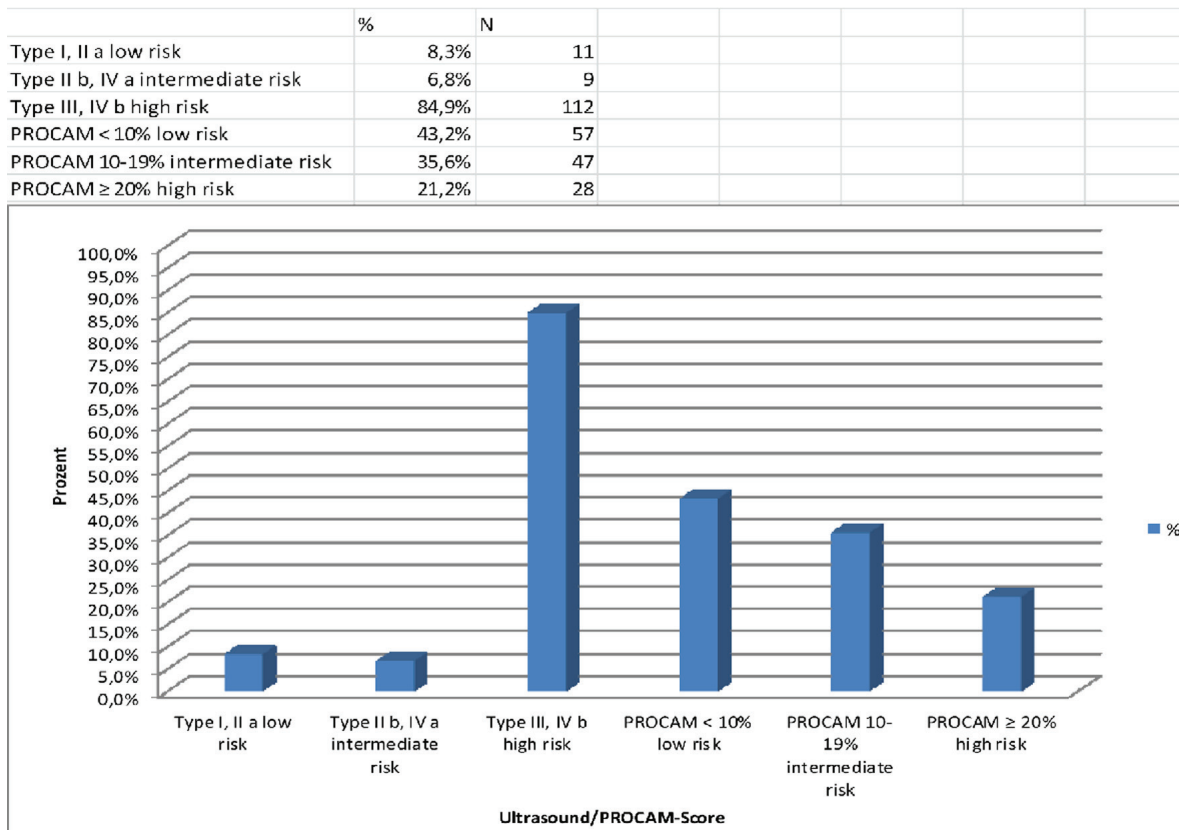


Figure 2. Distribution of patients with a cardiovascular event (n = 132) among risk categories defined by ultrasound and by PROCAM. PROCAM: the Prospective Cardiovascular Munster Study.

Confirmed coronary angiography findings were available in 297 subjects. In patients with a type III/IVb finding on ultrasound, the PPV for a coronary stenosis was 64%, in one cut-off ≥ 30% stenosis a PPV of 76% and for a cut-off of sclerosis 88%.

Several studies have shown that non-significant coronary artery stenosis is associated with an increased risk of heart attack [24-27]. It therefore appears important to diagnose and treat atherosclerosis at an earlier, clinical asymptomatic stage in order to

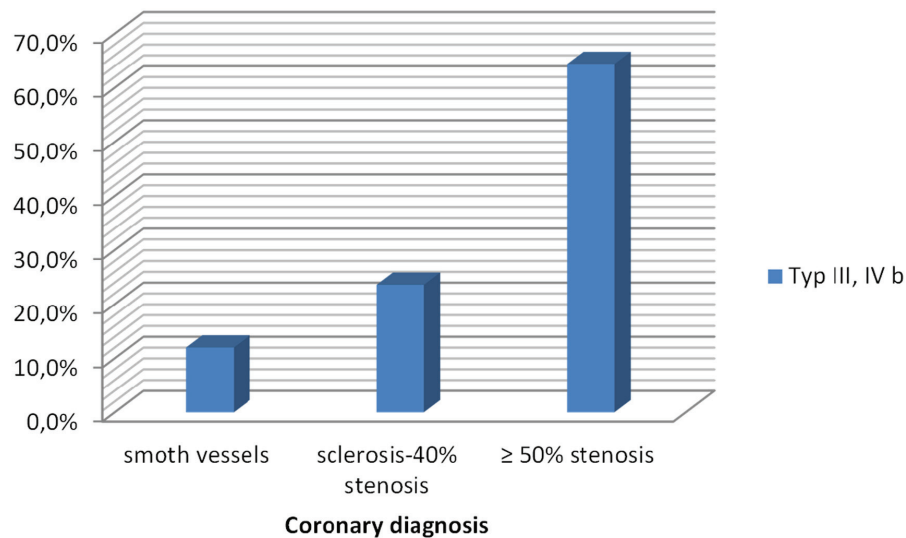


Figure 3. Coronary findings in the presence of a type III - IVb finding on ultrasound.

avoid or postpone cardiovascular events.

Our follow-up examinations showed that progression of atherosclerosis rarely occurs with statin treatment; regression can often be measured. A statistical analysis of this has not yet been carried out so far in our institution. The follow-up examination of the sick patients showed that the vast majority (85.4%) was not treated and was not detected with the PROCAM score. According to Assmann et al, 45% of infarct patients had a low PROCAM risk [19]. In cardiovascular prevention, it therefore seems sensible not only to determine the risk factors, but to measure the extent of the disease, the atherosclerosis. In the European Society of Cardiology (ESC) guidelines subjects with carotid plaques are classified to have a very high risk, but without giving a quantification [28, 29]. This study with age-related cut-off values for the TPA, taking into account the maximum plaque thickness, could help to reduce over therapy.

Conclusions

The determination of the plaque burden on the carotid artery using the described method is inexpensive, in principle available everywhere, easy to carry out, without side effects and improves the prediction or the exclusion of a CAD compared to the plaque area measurement alone or the risk stratification with the PROCAM score. If there is no type III or IVb finding on ultrasound, the probability of CAD with an NPV of 99% is very unlikely. Advanced atherosclerosis should be treated with statins.

Acknowledgments

None to declare.

Financial Disclosure

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Conflict of Interest

The authors declare that there is no conflict of interest.

Informed Consent

All patients provided informed consent.

Author Contributions

WB and MR discussed the approach and the findings of this study with AA intensively, and gave AA valuable feedback. All examinations as well as the statistical evaluation have been done by AA.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

Abbreviations

ROC: receiver operating curves; AUC: area under the curve; SE: sensitivity; SP: specificity; TPA: total plaque area (carotid plaque); PROCAM: the Prospective Cardiovascular Munster Study; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; Prev: prevalence; CAD: coronary artery disease

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