Total atherosclerotic burden by whole body magnetic resonance angiography predicts major adverse cardiovascular events

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ABSTRACT

Objective: The purpose of the present study was to investigate the relationship between the Total Atherosclerotic Score (TAS), a measurement of the overall atherosclerotic burden of the arterial tree by whole body magnetic resonance angiography (WBMRA), and the risk of major adverse cardiovascular events (MACE), defined as cardiac death, myocardial infarction, stroke and/or coronary revascularization, assuming that TAS predicts MACE.

Methods and results: 305 randomly selected 70 year-old subjects (47% women) underwent WBMRA. Their atherosclerotic burden was evaluated and TAS > 0, that is atherosclerotic changes, were found in 68% of subjects. During follow-up (mean 4.8 years), MACE occurred in 25 subjects (8.2%). Adjusting for multiple risk factors, TAS was associated with MACE (OR 8.86 for any degree of vessel lumen abnormality, 95%CI 1.14 e 69.11, p = 0.037). In addition, TAS improved discrimination and reclassification when added to the Framingham risk score (FRS), and ROC (Receiver Operator Curve) increased from 0.681 to 0.750 (p = 0.0421).

Conclusion: In a population-based sample of 70 year old men and women WBMRA, with TAS, predicted MACE independently of major cardiovascular risk factors.

1. Introduction

Identifying individuals with atherosclerosis in need of preventive treatment is an important task. Numerous tests and examinations [1–5] have been suggested to improve risk stratification as an addition to scoring systems, such as the Framingham Risk Score (FRS) [6].

The ultra-fast high-performance gradient system with the bolus chase method has enabled whole body magnetic resonance angiography (WBMRA), allowing visualization of the majority of the arterial tree by means of a single contrast-injection [7]. The method is continuously improving, but so far, the atherosclerotic burden and its relation to outcome have not been investigated [8,9].

The Total Atherosclerotic Score (TAS), established with WBMRA, has been proposed to estimate systemic atherosclerosis [10].

The purpose of the present study was to investigate the relationship between TAS and the risk of major adverse cardiovascular events (MACE), assuming that TAS predicts MACE. Other markers of atherosclerosis (Ankle Brachial Index (ABI), Carotid Intima Media Thickness (CIMT), and evidence of plaques in the carotid arteries on ultrasound) were also evaluated for their ability to predict MACE.

2. Methods

2.1. Study population

After approval by the Ethics Committee of the University of Uppsala, and written consent by the participants, WBMRA was performed on 306 subjects, aged 70, who were chosen consecutively from the population-based PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study [11]. They were thoroughly examined, as displayed in Table 1, and underwent the WBMRA within 3–22 months (mean 16 months) from study enrollment. 305 WBMRA-examinations were assessable: Previous studies have demonstrated this sub-population to be representative of the total epidemiological cohort [12].

2.2. Image acquisition

The WBMRA examination was performed with a 1.5 Tesla (T) scanner. The subjects were scanned in the supine position. The
WBMRA examination was attained from 4 overlapping combined stations giving a maximum covering length of 171 cm, starting at the Circle of Willis. Breath-holding was performed in the abdominal station: Thigh compression was not applied. A 3D RF-spoiled, T1-weighted gradient echo acquisition was performed prior to and after injection of 40 ml of Gadodiamide. The stations were scanned sequentially from head to feet; each scan took 87 s to perform. This has been described elsewhere [13].

2.3. Image analysis

As reported previously [10] a scoring system, TAS, was developed prospectively by dividing the arterial tree into 26 vessel segments, categorized into five territories: 1. The carotids; 2. The aorta; 3. The renal arteries; 4. The pelvic and upper legs; and, 5. The lower legs.

Each segment of vessel lumen was evaluated, in the original coronal images, by a radiologist (TH), with 5 years experience in MRI; only the most severe stenosis was scored. A normal vessel segment scored null points; stenosis less than 50% scored one point, even the slightest irregularity of the vessel wall acknowledged; and, luminal reduction of 50% or more, including occlusions, scored two points (Fig. 1). The obtained score was divided by the maximum possible score. This quotient was multiplied by 100, generating a maximum score per territory of 100. TAS was calculated as the sum of all five territories, giving a maximum total score of 500, and a lowest possible score, in case of abnormality, of 5.

Reproducibility and reliability of the scoring system have previously been rated good to excellent [12].

2.4. Other parameters

The data needed to determine multiple risk factors was obtained at study enrollment [11]. These data were: sex; waist circumference; body-mass index; fasting blood glucose; systolic blood pressure; HDL and LDL-cholesterol; total cholesterol; serum triglycerides; smoking; and, hsCRP. FRS was calculated [6]. Diabetes was defined as the use of antidiabetic drugs or fasting blood glucose >6.2 mmol/l. Calculation of ABI, analysis of CIMT, and assessment of carotid plaques were done by standardized methods that have been described previously [14,15].

Table 1
Baseline characteristics in the WBMRA samples.

<table>
<thead>
<tr>
<th>WBMRA study cohort</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Subjects</td>
</tr>
<tr>
<td>Females</td>
<td>47 %</td>
</tr>
<tr>
<td>Height</td>
<td>169 ± 9.4 cm</td>
</tr>
<tr>
<td>Weight</td>
<td>77 ± 14 kg</td>
</tr>
<tr>
<td>BMI</td>
<td>27 ± 4 kg/m²</td>
</tr>
<tr>
<td>SBP</td>
<td>149 ± 22 mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>78 ± 10 mmHg</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>5.4 ± 1.0 mmol/l</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>3.3 ± 0.8 mmol/l</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.5 ± 0.4 mmol/l</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>1.3 ± 0.6 mmol/l</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>5.3 ± 1.6 mmol/l</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>8 %</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 %</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 %</td>
</tr>
<tr>
<td>Previous CAGB or PCI</td>
<td>4 %</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>7 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 %</td>
</tr>
<tr>
<td>FRS</td>
<td>11.1 ± 3.3</td>
</tr>
<tr>
<td>hsCRP</td>
<td>2.3 ± 4.5 mg/l</td>
</tr>
<tr>
<td>ABI right side</td>
<td>1.15 ± 0.16 mm</td>
</tr>
<tr>
<td>ABI left side</td>
<td>1.14 ± 0.15 mm</td>
</tr>
<tr>
<td>CIMT</td>
<td>0.90 ± 0.17 mm</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>19 %</td>
</tr>
<tr>
<td>Ca-antagonists</td>
<td>12 %</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>8 %</td>
</tr>
<tr>
<td>Statins</td>
<td>13 %</td>
</tr>
<tr>
<td>A2Blockers</td>
<td>8 %</td>
</tr>
<tr>
<td>Diuretics</td>
<td>12 %</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2 %</td>
</tr>
<tr>
<td>ASA</td>
<td>18 %</td>
</tr>
</tbody>
</table>

Means ± standard deviation are given.
Abbreviations: BMI — Body Mass Index; SBP — Systolic Blood Pressure; DBP — Diastolic Blood Pressure; HDL — high-density lipoprotein; LDL — low-density lipoproteins; MI — myocardial infarction; CAGB — coronary artery bypass graft surgery; PCI — percutaneous coronary interventions; FRS — Framingham risk score; hsCRP — high sensitivity C-reactive protein; ABI — ankle brachial index; CIMT — carotid intima media thickness; ACE — angiotensin converting enzyme; A2 — angiotensin 2; ASA — acetylsalicylic acid.

Fig. 1. Illustration of WBMRA with scoring examples. Whole body magnetic resonance angiography (WBMRA) illustrated by Maximum Intensity Projection Images of the four stations (a) on a subject scoring 102.5 points in the total atherosclerotic score. The enhanced areas exemplify given scores in the original coronary images: (b) Arrow points to a normal right common carotid artery. (c) Arrow points to abdominal aorta with irregular vessel wall scoring 1 point, and (d) arrow points to severe stenosis (>50% of the diameter) in the left external iliac artery (2 points).
2.5. Follow-up

Access to all medical charts from the public health care within the municipality of Uppsala was obtained, including institutional and non-institutional care. After a follow-up period of 4–8 years (mean 4.8 years) the medical charts were scrutinized. MACE was defined as cardiac death, a hospital diagnosis of MI, or stroke, and/or revascularization with Coronary Artery Bypass Graft surgery (CABG) or Percutaneous Coronary Interventions (PCI). MACE was only reported once per subject in the study.

2.6. Statistical analysis

Of 305 analyzed subjects, 99 (32.5%) had normal vessels on WBMRA (TAS = 0), and in the remaining subjects TAS varied between 5 and 136.25 (mean 41.1, median 35) [10]. To obtain three similarly sized groups, the subjects with TAS > 0 were divided into two groups, separated by the median TAS value. A chi-square test was performed for the three groups (TAS = 0, TAS 5–35, and TAS > 35) and their relations to MACE.

Logistic regression analysis was performed to identify associations between MACE and TAS, in addition to other markers of atherosclerosis, including traditional risk factors. Three hierarchical sets of models were investigated (1. adjusted for sex; 2. adjusted for sex and FRs; and 3. adjusted for sex and multiple risk factors). TAS was evaluated by trend test using the three models described above. The odds ratio (OR) was calculated for subjects with TAS > 0 compared to subjects with normal vessels.

The value of adding TAS to the FRs was evaluated by C-statistics and ROC (Receiver Operator Curve). Tests of re-classification (NRI) and integrated discrimination improvement (IDI) were done according to the method proposed by Pencina et al. [16]. For the NRI analyses, three MACE risk groups were formed: <6% (low risk); 6–10% (intermediate risk); and >10% (high risk), based on the result of about 8% of subjects having an MACE during the follow-up period of 4.8 years.

In an alternative setting, resembling clinical routine with focus on the degree of each stenosis, the subjects were classified into three groups: one group with no abnormalities (n = 99); one group with no significant stenosis, i.e. 1–49% luminal reduction (n = 113); and one group with at least one significant stenosis, i.e. 50% or greater luminal reduction (n = 92).

P-values < 0.05 from two-sided tests were considered statistically significant. The statistical software package Stata 11 (Stata Corporation, College Station, TX, USA) was used.

3. Results

During follow-up, MACEs occurred in 25 of the 305 subjects (22 men and 3 women). Seven subjects suffered a stroke, 13 had an MI, and 16 underwent PCI or CABG (11 of these were also included in the MI-group). One participant died during PCI.

3.1. TAS vs. MACE

The presence of atherosclerosis in any segment (TAS > 0) predicted MACE when adjusted for sex, sex plus FRs, or sex plus multiple risk factors. Odds Ratios (OR) are presented in Table 2.

Adjusting for CIMT in the model including sex and FRs did result in a perfect fit for TAS > 0 in the model and therefore no OR could be calculated. Thus, adjustment for CIMT improved the predictive power for TAS. Adjusting for carotid plaque occurrence at ultrasound did only marginally change the OR for TAS > 0 (OR 8.48, 96% CI 1.09–65.93 following additional adjustment).

Adding the variable "previous MACE", including prior myocardial infarction, stroke and coronary revascularization, to the model adjusting for multiple risk factors did not substantially alter the OR for TAS > 0 (now OR 8.51, 95%CI 1.09–66.4). Neither did substituting SBP with pulse pressure and mean arterial blood pressure induce any major change in the OR for TAS > 0 (now OR 8.13, 95%CI 1.02–64.50).

The atherosclerotic scores (AS) for the five separate territories, used to calculate TAS, were applied in five separate models adjusted for sex and FRs, in order to evaluate individual predictive values. Only for the carotid arteries, territory 1, TAS > 0 was significantly related (p < 0.05) to future MACE (OR 2.41, 95%CI 1.01–5.75). A similar OR was seen for TAS > 0 in the aorta (2.32, 95%CI 0.97–5.53), although not significant (p = 0.09), and the associations between MACE and the other regions were considerably weaker (OR 1.39, 95%CI 0.46–4.17 for the kidneys, OR 1.68, 95%CI 0.71–3.98 for the upper legs and OR 1.24, 95%CI 0.51–2.99 for the lower legs).

The addition of TAS to the FRs, as a predictor of MACE, increased the C-statistic ROC (Receiver Operator Curve) from 0.681 (95%CI 0.58–0.78) to 0.750 (95%CI 0.66–0.83), p = 0.04. The corresponding IDI was 0.024, standard error 0.0098 (p = 0.015).

When the TAS variable was added 7 of 14 subjects with MACE were moved from the low or intermediate risk groups to the high risk group, and 66 of 164 subjects without MACE were moved from the intermediate or high risk groups to the low risk group (Table 3).

MACE was significantly more frequent in subjects with TAS > 0–35 and TAS > 35 respectively, compared with subjects with normal vessels (p = 0.003) (Fig. 2).

Table 2

<table>
<thead>
<tr>
<th>TAS-groups</th>
<th>Models adjusted for sex</th>
<th>C-statistics</th>
<th>Models adjusted for sex and FRs</th>
<th>Models adjusted for sex and multiple factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trend test  for the 3 TAS-groups</td>
<td>OR 95%CIC</td>
<td>p-value</td>
<td>OR 95%CIC</td>
<td>p-value</td>
</tr>
<tr>
<td>TAS &gt; 0p vs. 0p</td>
<td>2.16 1.17–3.99 0.014</td>
<td>1.89 1.01–3.55 0.046</td>
<td>2.07 1.06–4.04 0.034</td>
<td>0.69</td>
</tr>
<tr>
<td>TAS 1–35p vs. 0p</td>
<td>10.15 1.34–77.01 0.025</td>
<td>8.80 1.15–67.29 0.036</td>
<td>8.66 1.14–69.11 0.037</td>
<td>0.66</td>
</tr>
<tr>
<td>TAS &gt; 35p vs. 0p</td>
<td>9.19 1.14–74.09 0.023</td>
<td>8.94 1.10–72.45 0.040</td>
<td>8.30 1.01–68.53 0.049</td>
<td>0.67</td>
</tr>
<tr>
<td>CIMT (mm)</td>
<td>11.03 1.40–86.88 0.023</td>
<td>8.67 1.08–65.42 0.042</td>
<td>9.48 1.15–78.37 0.037</td>
<td>0.67</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>11.84 0.96–145.2 0.053</td>
<td>4.80 0.32–71.78 0.26</td>
<td>5.93 0.37–95.44 0.21</td>
<td>0.61</td>
</tr>
</tbody>
</table>

Logistic regression models of relations between four groupings of TAS, as independent variables for MACE risk (n = 25) during 4.8 years of follow-up. The first set of models was adjusted for sex; the second set of models were adjusted for sex and the FRs; the third set of models were adjusted for sex and multiple individual risk factors: sex, waist circumference, body mass index, fasting blood glucose, systolic blood pressure, HDL and LDL-cholesterol, serum triglycerides, smoking and hs-C-reactive protein. In all of these three sets of models, atherosclerosis was investigated as a continuous variable (OR per SD). Sample size: 305. Abbreviations: p – points; TAS – Total Atherosclerotic Score; CIMT – carotid intima-media; ABI – ankle brachial index; FRs – Framingham risk score; MACE – major adverse cardiovascular events; OR – odds ratio; CI – confidence interval; SD – standard deviation; AUC – area under the curve with C-statistics for unadjusted models.

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TAS (divided in three groups; 0, >0–35, or ≥35) predicted MACE in a linear trend test, also when adjusted for sex, sex plus FRS, or sex plus multiple risk factors. When the two groups with atherosclerosis (TAS > 0) were compared with the group without atherosclerosis (TAS = 0), both of the atherosclerotic groups demonstrated a considerably higher risk compared to the group with TAS = 0 (Table 2).

3.2. Stenosis vs. MACE

In the alternative setting, 12 subjects experienced an MACE in each group with atherosclerosis (no significant stenosis, and significant stenosis), compared to only one subject in the group with normal vessels (p = 0.005). Both groups with visible atherosclerosis on WBMRA were significantly associated with future MACE, independently of multiple risk factors (OR 8.60, 95%CI 1.05 to 69.8, p = 0.044 for the group without significant stenosis and OR 9.36, 95%CI 1.11 to 78.7, p = 0.039 for the group with significant stenosis compared to the group with normal vessels).

3.3. Other markers of atherosclerosis vs. MACE

Occurrence of plaque in the carotid arteries at ultrasound was related to total TAS (Spearman’s Rho 0.28, p < 0.001), as well as to TAS in the carotid arteries only (Spearman’s Rho 0.29, p < 0.001).

Neither CIMT nor ABI, nor the presence of ultrasound detected plaques, were significantly related to risk of future MACE (Table 2).

When the presence of ultrasound detected plaques variable was added to FRS 3 of 14 subjects with MACE were moved from the low or intermediate risk groups to the high risk group, and 29 of 150 subjects without MACE were moved from the intermediate or high risk groups to the low risk group (p = 0.175).

4. Discussion

TAS was a powerful predictor of MACE, with a more than eightfold risk of developing MACE in subjects with any irregularity in the arteries on WBMRA. Thus, the degree of stenosis seems to be of minor importance in predicting MACE. Only one subject with normal arteries suffered an MACE during the follow-up suggesting good test specificity.

The golden standard of angiography is digital subtraction angiography (DSA) where ionizing radiation, as well as contrast agents, is used. WBMRA has not been validated against DSA as a whole but numerous studies have validated specific regions, such as renal and peripheral MRA, with fine results [17,18].

To the best of our knowledge, this is the first time that WBMRA has been evaluated in a prospective study in a general population. The strong correlation between atherosclerotic burden and future MACE makes the scoring system a plausible candidate for improving risk assessment. The present study contained subjects from all kinds of risk groups, including subjects with previous MACE. A possible further development could be to evaluate this method in another setting; focusing on primary prevention.

Plaque prevalence in the separate arterial territories has previously shown good correlation to the FRS [10]; in this study the territories predictive power on their own has also been analyzed. The OR’s being lower for the separate territories and only significant in the first (carotid) territory suggests that it is the prevalence of atherosclerosis in any part of the body rather than specific locations that is correlated with cardiovascular outcome, although atherosclerosis in the upper parts of the body seems to be more predictive than in the lower parts.

ABI, CIMT, and the presence of carotid plaques are often suggested as additional methods to strengthen the somewhat coarse scoring systems, using traditional risk factors and circulating biomarkers [19]. Even though these parameters have proved to predict cardiovascular events in other studies [2,3], they were not significantly related to risk of future MACE in the present study, whereas TAS was.

Imaging methods hold the advantage of not only elucidating risks in evaluation, but also depicting the presence of pathology in asymptomatic subjects, and have been advocated to become mandatory in assessing atherosclerotic risk [20]. This notion might be supported by the results in the present study.

The present study only depicted the vessel lumen, entailing the risk of missing positively remodeled plaques, a well known weakness to all types of lumenographic examinations [21]. Despite not identifying positively remodeled plaques or differentiating between types of plaques, there was a significant association between the total burden of lumen affecting plaques and MACE and hardly any MACEs were found in the subjects without identified pathology in the present study. These results indicate a future value in WBMRA in spite of not analyzing plaque composition or vulnerability.

Dark blood-WBMRA, based on a T1-weighted-SPACE sequence, has recently been put forward as an alternative method to avoid contrast-enhancement and enabling evaluation of the vessel wall [22]. However, the mean imaging time period in that study was close to 1 h, which precludes its feasibility. Faster non-contrast enhanced MRA methods, have been described [23] but are not yet applied in whole-body settings.

![Fig. 2. Incidence of MACE at a mean follow-up of 4.8 years (percentage within each group). A relation between the cumulative incidence of MACE for the different categories of TAS (p = 0.001). The y-axis demonstrates percentage within each group. Abbreviations: MACE – major adverse cardiovascular events; TAS – total atherosclerotic score.](image-url)
Technological improvements in WBMRA make a significant difference in the assessment of peripheral arteries, where sub-mm voxels permit as many as three pixels per vessel enabling correct evaluation [24]. In a previous publication [12], analyzing the present material, the total success rate of vessel evaluation was reported as 99.3%, and dropped to 98.6% in the lower leg. Further developments of the imaging technique might render TAS an even stronger predictor.

5. Limitations

The described population consisted of elderly Caucasians. The age being constant in the cohort eliminated a variable in the statistics but the results need to be confirmed in other populations as well.

Adding thigh compression might improve imaging, although vein overlapping was not a problem in this study. The limited resolution in the present study protocol might have caused errors in evaluation of the smaller arteries.

The time between obtaining the FRS-information and performing the WBMRA of 3–22 months (mean 16 months) was rather long, but should likely have limited adverse effects on the results of the study since atherosclerosis is a slowly developing degenerative disease [25]. The sample-size was determined by logistic reasons. Despite the low number of MACES, the present study identifies subjects with high risk of future MACE.

Another limitation of the study is the fact that MACE occurs in the brain and the heart, but these areas of the body were not examined. An extension of the examination protocol could include evaluation of cardiac function and ischemic changes in heart and brain parenchyma.

6. Conclusion

In conclusion, the atherosclerotic burden, evaluated with TAS on WBMRA, predicted MACE independently of major cardiovascular risk factors in a population-based sample of 70-year-old men and women.

Sources of funding

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Disclosures

L.J. is a part time employee at Astra Zeneca R&D, Mölndal, Sweden.

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