Association of High Ankle Brachial Index With Incident Cardiovascular Disease and Mortality in a High-Risk Population

Eva J.E. Hendriks, Jan Westerink, Pim A. de Jong, Gert J. de Borst, Hendrik M. Nathoe, Willem P.Th.M. Mali, Yolanda van der Graaf, Yvonne T. van der Schouw, Joline W. Beulens; SMART Study Group

Objective—The objective of this present study is to determine whether high ankle brachial index (ABI) as compared with ABIs within reference limits is associated with an increased incidence of cardiovascular disease (CVD) events and all-cause mortality in a high-risk population and whether this association is the same for patients with and without diabetes mellitus or prevalent CVD.

Approach and Results—Seven thousand five hundred and thirty-eight patients with ABI>0.9 and either prevalent CVD or a high risk for CVD were selected from the Second Manifestations of Arterial Disease (SMART) study. Three hundred and thirty-six participants (4.5%) had high ABI (≥1.4 or incompressible). Higher age, male sex, higher body mass index, and diabetes mellitus were associated with higher prevalences of high ABI; smoking and higher non–high-density lipoprotein levels were associated with lower prevalences of high ABI. Cox proportional hazards models were fitted assessing the association of high ABI (as compared with ABI 0.9–1.4) with the risk of myocardial infarction, stroke, cardiovascular death, the combined outcome of these 3, and total mortality (median follow-up 6.9 years). After multivariable adjustment, high ABI was associated with an increased risk of myocardial infarction (hazard ratio 1.83 [95% confidence interval 1.22–2.76]), but not with stroke (hazard ratio 0.86 [95% confidence interval 0.44–1.69]), cardiovascular (hazard ratio 1.14 [95% confidence interval 0.70–1.84]), or all-cause mortality (hazard ratio 0.95 [95% confidence interval 0.67–1.34]). Associations of high ABI with CVD outcomes tended to be stronger in patients with diabetes mellitus but without statistically significant interactions.

Conclusions—In a high-risk population, the presence of an ABI≥1.4 was associated with an increased risk for myocardial infarction, but not with stroke, all-cause, or vascular mortality. (Arterioscler Thromb Vasc Biol. 2016;36:412-417. DOI: 10.1161/ATVBAHA.115.306657.)

Key Words: ankle brachial index ▪ arterial stiffness ▪ cardiovascular disease risk factors ▪ cardiovascular events ▪ vascular disease

The ankle brachial index (ABI) is the ratio between systolic blood pressure measured at the ankle (posterior tibial and dorsalis pedis artery) and the brachial artery. It is traditionally used to diagnose peripheral artery disease, for which a cutoff value of ≤0.90 is commonly used. People with peripheral artery disease, even when asymptomatic, have a worse prognosis than people with an ABI within reference limits in terms of risk of death and cardiovascular events.

Much less is known about high ABI (≥1.40). High ABIs are generally believed to arise because of medial arterial calcification and may be a marker for vascular stiffness. High ABI has been reported to be associated with male sex, diabetes mellitus and hypertension and inversely associated with smoking and hyperlipidemia, but the high ABI patient group remains poorly characterized.

The ABI collaboration published a meta-analysis in 2008, showing a U-shaped association between ABI and mortality, which indicates that not only low ABI values, but also high ABIs convey excess risk as compared with ABIs within reference limits. High ABI has also been associated with increased risk of other outcomes than mortality, such as incident cardiovascular disease (CVD), congestive heart failure, stroke, and higher left ventricular mass. It is hypothesized that high ABI may be a reflection of increased vascular stiffness that increases the risk of adverse outcomes. However, prospective studies that describe confounder-adjusted analyses are scarce,
and results are inconsistent. Inconsistencies may in part be because of different relationships of ABI across different populations. It has been suggested that the association of ABI with CVD is only U-shaped in patients with type 2 diabetes mellitus and that a high ABI does not convey excess risk in other individuals.

The objective of this present study is 2-fold. First, we aim to characterize the group with high ABI compared with the group with ABI within reference limits in terms of their cardiovascular risk factors. Second, we aim to determine whether high ABI (≥1.40) as compared with ABI 0.9–1.40 is associated with an increased incidence of CVD events and all-cause mortality in a high-risk population, in which a majority of patients have clinically manifest CVD. As an additional objective, we wish to study whether this association is similar in subgroups defined by the presence of prevalent CVD and diabetes mellitus.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement. In short, 7542 patients with ABI>0.9 and either prevalent CVD or a high risk for CVD were selected from the Second Manifestations of Arterial Disease (SMART) study. Cox proportional hazards models were fitted assessing the association of high ABI (as compared with ABI 0.9–1.4) with the risk of myocardial infarction (MI), stroke, cardiovascular death, the combined outcome of these 3, and total mortality (median follow-up 6.9 years).

Results

Baseline Characteristics

Of 7542 included patients, 7203 (95.5%) had ABIs within reference limits and 339 (4.5%) had high ABI (≥1.40 or incompressible; Figure). Patients with high ABI were older (average 58.8 versus 55.4 years) and more often male (86%) compared with those with ABIs within reference limits (66%). Other characteristics are described in Table 1.

Determinants of High Ankle Brachial Index

Increasing age and male sex were associated with having high ABI (odds ratio [OR] 10 years 1.26 [95% confidence interval [CI] 1.15–1.39] and 3.00 [95% CI 2.20–4.09], respectively). Diabetes mellitus (OR 1.54 [95% CI 1.21–1.98]) and body mass index (OR 1.04 [95% CI 1.01–1.06]) were associated with high ABI at baseline after age and sex adjustment. Risk factors significantly associated with having ABIs within reference limits were a higher non-HDL cholesterol (OR 0.89/ mmol/L [95% CI 0.82–0.98]) and smoking (former versus never OR 0.70 [95% CI 0.55–0.90], current versus never OR 0.32 [95% CI 0.22–0.46]). The other characteristics studied (hypertension, systolic blood pressure, pulse pressure, estimated glomerular filtration rate, Kidney Disease Outcomes Quality Initiative category, and physical activity) were not associated with high ABI at baseline (Table 2). Adjustment for medical treatment with lipid-lowering drugs or blood pressure–lowering drugs did not alter the results of non-HDL cholesterol and systolic blood pressure, respectively.

Association Between High Ankle Brachial Index and Cardiovascular Events and Mortality

During a median follow-up of 6.9 (interquartile range 3.7–10.2) years, 292 patients had an MI, 216 patients had a stroke, and 680 patients died, 302 of whom from a vascular cause. We counted 694 cases for our compound outcome, with incidences of 13.2 (95% CI 12.4–14.0)/1000 person years and 19.0 (95% CI 13.4–24.7)/1000 person years in the reference ABI group and the high ABI group, respectively. The associations between high ABI and our studied outcomes are provided in Table 3. With age and sex adjustment, only the model for MI showed significant associations. After multivariable adjustment, high ABI remained associated with a higher risk for MI (1.83 [95% CI 1.22–2.75]). Results did not change when adjusting for coronary heart disease instead of CVD history. No associations were found for any of the other outcomes. In the sensitivity analysis excluding patients with peripheral artery disease, the association of high ABI with the compound outcome did not change (hazard ratio [HR] 1.22 [95% CI 0.89–1.66] versus 1.24 [95% CI 0.91–1.68] for the full cohort).

In our stratified analyses, we observed that high ABI tended to be a stronger risk factor for the compound cardiovascular outcome in patients with diabetes mellitus, although HRs were not statistically significant, and neither was the interaction term (Table 4). Similarly, high ABI tended to be a stronger risk factor for the compound cardiovascular outcome in patients with prevalent CVD but without statistical significance. For myocardial infarction, high ABI was associated...
with higher risk in patients with diabetes mellitus (HR 2.44 [95% CI 1.26–4.73]) and in patients with prevalent CVD at baseline (HR 1.98 [95% CI 1.28–3.07]), but not in patients without diabetes mellitus (HR 1.54 [95% CI 0.91–2.62]) and patients without prevalent CVD at baseline (HR 1.04 [95% CI 0.32–3.40]), although the interaction terms did not reach statistical significance.

**Discussion**

In the present study in a population at high risk of CVD, age, male sex, high body mass index, and diabetes mellitus were associated with higher prevalence of high ABI, whereas smoking and higher non-HDL cholesterol were associated with a lower prevalence of high ABI. High ABI was associated with increased incidence of incident MI after multivariable adjustment, but not with stroke, vascular, or all-cause mortality, or the compound outcome, when compared with ABIs within reference limits. We found that a significant association existed between high ABI and MI among patients with diabetes mellitus that was not present in others, but no significant interaction by diabetes mellitus status was seen.

The risk factor profile we found might not be expected when considering high ABI as a marker of cardiovascular risk equivalent to low ABI. A lower rate of current or former smoking and dyslipidemia in people with high ABI have been previously reported.4,5,12,13 One previous study reported a lower prevalence of current smoking, as well as male sex and high body mass index, to be associated with progressing into high ABI,14 which is in line with our cross-sectional findings and suggests they might be real associations, not just epiphenomena induced by our cross-sectional design.

An explanation for lower rates of smoking among people with high ABI might be found in the association of risk factors with medial arterial calcification. Medial arterial calcification, a type of calcification that occurs in the middle layers of arteries, is reported to be associated with age, diabetes mellitus,
A person with high ABI has a 77% higher hazard of getting an MI compared with someone with ABIs within reference limits. Multivariable 2† 1.24 (0.91–1.68) 0.004 BMI (per 1 kg/m²) 1.04 (1.01–1.06) 0.004 Diabetes mellitus (type 1 or 2) 1.54 (1.21–1.98) <0.001 Sex (male) 3.00 (2.20–4.09) <0.001 Non-HDL cholesterol (per 1 mmol/L) 0.89 (0.82–0.98) 0.014 Hypertension (treated) 1.20 (0.96–1.49) 0.111 History of hypertension (treated or measured) 1.16 (0.93–1.46) 0.184 SBP (per 10 mmHg) 1.04 (0.99–1.10) 0.110 Pulse pressure (per 10 mm Hg) 1.02 (0.95–1.10) 0.590 eGFR (per 10 mL/min) 0.95 (0.88–1.02) 0.147 Renal insufficiency (eGFR <60 mL/min) 1.16 (0.84–1.61) 0.375 Smoking (former versus never) 0.70 (0.55–0.90) 0.005 Smoking (current versus never) 0.32 (0.22–0.46) <0.001 Physical activity (per 10 METs h/wk) 1.01 (0.98–1.03) 0.375

Table 2. Association Between Risk Factors and High Ankle Brachial Index in Patients With An Ankle Brachial Index ≥0.9

<table>
<thead>
<tr>
<th>Determinant (Predictor) of the Model</th>
<th>OR (95% CI) for Having High ABI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 y)</td>
<td>1.26 (1.15–1.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>3.00 (2.20–4.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (type 1 or 2)</td>
<td>1.54 (1.21–1.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (per 1 kg/m²)</td>
<td>1.04 (1.01–1.06)</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-HDL cholesterol (per 1 mmol/L)</td>
<td>0.89 (0.82–0.98)</td>
<td>0.014</td>
</tr>
<tr>
<td>History of hypertension (treated)</td>
<td>1.20 (0.96–1.49)</td>
<td>0.111</td>
</tr>
<tr>
<td>Hypertension (treated or measured)</td>
<td>1.16 (0.93–1.46)</td>
<td>0.184</td>
</tr>
<tr>
<td>SBP (per 10 mmHg)</td>
<td>1.04 (0.99–1.10)</td>
<td>0.110</td>
</tr>
<tr>
<td>Pulse pressure (per 10 mm Hg)</td>
<td>1.02 (0.95–1.10)</td>
<td>0.590</td>
</tr>
<tr>
<td>eGFR (per 10 mL/min)</td>
<td>0.95 (0.88–1.02)</td>
<td>0.147</td>
</tr>
<tr>
<td>Renal insufficiency (eGFR &lt;60 mL/min)</td>
<td>1.16 (0.84–1.61)</td>
<td>0.375</td>
</tr>
<tr>
<td>Smoking (former versus never)</td>
<td>0.70 (0.55–0.90)</td>
<td>0.005</td>
</tr>
<tr>
<td>Smoking (current versus never)</td>
<td>0.32 (0.22–0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physical activity (per 10 METs h/wk)</td>
<td>1.01 (0.98–1.03)</td>
<td>0.635</td>
</tr>
</tbody>
</table>

and renal disease and also with lower rates of smoking.15,16 High ABIs are generally believed to arise because of medial arterial calcification.3 In that sense, our results are in line with previous studies on medial arterial calcification. However, only one study in patients with type I diabetes mellitus has assessed the relationship between high ABI and medial arterial calcification17 and found a strong relation between high ABI and medial arterial calcification.

We found a clear association of high ABI with incident MI even after adjusting for risk factors, whereas we did not find an association with any of the other outcomes. For the compound CVD outcome, only the crude association was significant, indicating that the risk factors may fully explain the compound CVD outcome (their main outcome) in nondiabetic patients could not be reliably derived.9 The second study, however, showed significant associations with all-cause and cardiovascular mortality among patients with diabetes mellitus and a lack thereof in patients without diabetes mellitus, but without showing a significant interaction.22 This is similar to what we found when stratifying our myocardial infarction analysis by diabetes mellitus status. Although the evidence does not warrant a conclusion that the relationship truly is different in diabetes mellitus patients, the effect size estimates have so far been higher among patients with diabetes mellitus.9,22 It is hypothesized that in patients with diabetes mellitus, high ABI co-occurs with a heavy burden of risk factors more frequently and that despite adjustment for risk factors, (residual) confounding might explain the stronger relationships.5,9,22 Future studies could compare patients with type 1 and type 2 diabetes mellitus because patients with type 1 diabetes mellitus typically have much less co-occurring risk factors. If patients with type 1 diabetes mellitus are found to have a similar high ABI–CVD relation, it is

Table 3. The Associations Between High ABI and Our Studied Outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>Compound Outcome, 694 Events (44 High ABI)</th>
<th>MI, 292 Events (26 High ABI)</th>
<th>Stroke, 216 Events (9 High ABI)</th>
<th>CVD Mortality, 302 Events (18 High ABI)</th>
<th>All-Cause Mortality, 680 Events (34 High ABI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI) P Value</td>
<td>HR (95% CI) P Value</td>
<td>HR (95% CI) P Value</td>
<td>HR (95% CI) P Value</td>
<td>HR (95% CI) P Value</td>
</tr>
<tr>
<td>Age/sex adjusted</td>
<td>1.17 (0.86–1.59) 0.309</td>
<td>1.76 (1.18–2.65) 0.006</td>
<td>0.77 (0.39–1.50) 0.435</td>
<td>1.05 (0.65–1.70) 0.831</td>
<td>0.88 (0.62–1.24) 0.466</td>
</tr>
<tr>
<td>Multivariable 1*</td>
<td>1.28 (0.94–1.74) 0.116</td>
<td>1.89 (1.26–2.84) 0.002</td>
<td>0.86 (0.44–1.69) 0.667</td>
<td>1.20 (0.74–1.94) 0.466</td>
<td>0.98 (0.69–1.38) 0.897</td>
</tr>
<tr>
<td>Multivariable 2†</td>
<td>1.24 (0.91–1.68) 0.179</td>
<td>1.83 (1.22–2.75) 0.004</td>
<td>0.86 (0.44–1.69) 0.666</td>
<td>1.14 (0.70–1.85) 0.595</td>
<td>0.95 (0.67–1.34) 0.761</td>
</tr>
</tbody>
</table>

ABI indicates ankle brachial index; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MET, metabolic equivalent of task; OR, odds ratio; and MI, myocardial infarction.

*Adjusted for sex, age, smoking status, non-HDL cholesterol, and prevalent cardiovascular disease.
†Adjusted for sex, age, smoking status, diabetes mellitus status, non-HDL cholesterol, systolic blood pressure, eGFR, and prevalent cardiovascular disease. Example: A person with high ABI has a 77% higher hazard of getting an MI compared with someone with ABIs within reference limits.
unlikely that the stronger association among patients with diabetes mellitus is purely as a result of the higher co-existence of other risk factors.

Additional studies are needed to shed light on whether a high ABI is mainly a marker of a generally advanced stage of atherosclerosis or whether high ABI represents arterial stiffness that is detrimental in itself. Other measures of arterial stiffness, such as pulse wave velocity, are associated with a range of detrimental outcomes.24 Future studies should aim to verify the reported relationship of high ABI with medial arterial calcification and expand our knowledge of the relationships between diabetes mellitus, medial arterial calcification, arterial stiffness, and outcomes.

Strengths of this study include its large sample size and high event rate, the comprehensive risk factor information, completeness of data, and rigorous methods of follow-up and outcome assessment. Also, our population consisted mainly of patients with prevalent CVD, in contrast to the populations that have previously been studied, which consisted mainly of patients without clinical CVD or patients visiting a vascular laboratory or at high risk for peripheral artery disease.7,9,18,19

Limitations include the cross-sectional nature of the studied associations of risk factors with ABI and the small size of some of the subgroups, which, in combination with the low number of patients on the high end of the ABI distribution, may have resulted in insufficient power to show an interaction. It is not known how the co-occurrence of the pathologies of medial calcification and atherosclerosis in one patient influences the ABI. Although no data is available to support this, it is possible that the co-occurrence might sometimes result in an ABI between 0.9 and 1.4. On the other hand, when there is obstructive disease and considerable medial calcification at the same time, the result might still be an incompressible artery. Unfortunately, our data does not allow us to disentangle these effects. Finally, our population is a selected population consisting of a mix of primary prevention (high-risk) and secondary prevention patients. This limits the generalizability of our findings. Also, selection potentially induces a risk of selection bias when looking at risk factor associations with high ABI. This should be taken into account when interpreting our findings. Our stratified analyses provide some insight in the potential differences in the associations of high ABI with events between high-risk and prevalent disease patients.

Conclusions

In this cohort study of patients with a high risk for CVD, we found that high ABI (≥1.4) was associated with incident MI but not with (cardiovascular) mortality when compared with an ABI within reference limits (0.9–1.4). We found higher age, male sex, higher body mass index, diabetes mellitus, lower non-HDL cholesterol, and a lower prevalence of smoking to be associated with high ABI.

Table 4. Multivariable Adjusted Associations of High ABI With Cardiovascular Disease, Stratified by Diabetes and Prevalent CVD at Baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No of Patients</th>
<th>No of Events</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound outcome subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1485</td>
<td>190 (19)</td>
<td>1.57 (0.97–2.56)</td>
<td>0.067</td>
</tr>
<tr>
<td>No Diabetes mellitus</td>
<td>6057</td>
<td>504 (25)</td>
<td>1.08 (0.72–1.62)</td>
<td>0.714</td>
</tr>
<tr>
<td>Prevalent CVD at baseline</td>
<td>4967</td>
<td>567 (39)</td>
<td>1.32 (0.95–1.84)</td>
<td>0.096</td>
</tr>
<tr>
<td>No prevalent CVD at baseline</td>
<td>2575</td>
<td>127 (5)</td>
<td>0.72 (0.29–1.78)</td>
<td>0.476</td>
</tr>
<tr>
<td>Total population</td>
<td>7542</td>
<td>694 (44)</td>
<td>1.24 (0.91–1.68)</td>
<td>0.179</td>
</tr>
<tr>
<td>Myocardial infarction Subgroups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1485</td>
<td>75 (11)</td>
<td>2.44 (1.26–4.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>6057</td>
<td>217 (15)</td>
<td>1.54 (0.91–2.62)</td>
<td>0.109</td>
</tr>
<tr>
<td>Prevalent CVD at baseline</td>
<td>4967</td>
<td>235 (23)</td>
<td>1.98 (1.28–3.07)</td>
<td>0.002</td>
</tr>
<tr>
<td>No prevalent CVD at baseline</td>
<td>2575</td>
<td>57 (3)</td>
<td>1.04 (0.32–3.40)</td>
<td>0.943</td>
</tr>
<tr>
<td>Total population</td>
<td>7542</td>
<td>292 (26)</td>
<td>1.83 (1.22–2.75)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HR, hazard ratio; and SBP, systolic blood pressure. All models shown were adjusted for sex, age, smoking status, non-HDL cholesterol, SBP, and eGFR. The models stratified by diabetes mellitus status were also adjusted for prevalent CVD. The models stratified by prevalent CVD were also adjusted for diabetes mellitus status.

*P for interaction.

Acknowledgments

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High ankle brachial index (ABI) and incompressible ankle arteries are generally believed to arise as a result of medial arterial calcification and may be a marker for vascular stiffness. The high ABI patient group remains poorly characterized, and the risks associated with high ABI remain poorly understood. We were the first to study the risks associated with high ABI (≥1.4 or incompressible arteries versus ABI 0.9–1.4) in a high-risk and secondary prevention population. We found that the presence of high ABI was independently associated with an increased risk for myocardial infarction, but not with stroke, all-cause, or vascular mortality. High ABI should be considered a risk factor for myocardial infarction.
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**Materials and Methods**

**Population:**
The SMART (Second Manifestations of ARTerial disease) study is an on-going single center, prospective cohort study comprised of patients with CVD as well as patients at high risk for CVD. Details of the study have been described elsewhere. Starting in 1996, all patients aged 18-79 years that were newly referred to the University Medical Center Utrecht with either manifest vascular disease or important cardiovascular risk factors were asked to participate.

Patients were excluded if they suffered from terminal malignant disease, were not independent in daily activities, and/or had insufficient knowledge of the Dutch language to understand the patient information. The medical ethics review board at the University Medical Center Utrecht approved the study, and all participants gave their written informed consent.

For the present study, patients were eligible when they had ABIs within reference limits (>0.90 and <1.40) or high ABI (≥ 1.40), with a referral for clinically manifest vascular disease (either coronary artery disease (n=2998), cerebrovascular disease (n=1351) or PAD (n=214)) or who were referred for the treatment of cardiovascular risk factors (diagnosis of hyperlipidemia (n=1059), diabetes mellitus (type 1 and 2, n= 564) or hypertension (n=1356)). Patients with PAD could have ABIs >0.9 because the PAD referral group also includes patients with resting ABI within reference limits but a >20% drop in ABI after exercise, patients with previously abnormal ABIs that normalized after treatment, or patients with a diagnosis of PAD through other investigations (for example in case of referral with acute ischemia).

**Baseline measurements:**
At baseline, all SMART patients underwent a comprehensive vascular screening, consisting of physical examinations, laboratory measurements, imaging and a questionnaire on medical history, risk factors and medication use. Hypertension was defined as a SBP of ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg (mean of 2 blood pressure measurements) or use of antihypertensive medication. A history of diabetes mellitus was defined as either a referral diagnosis of diabetes mellitus, self-reported diabetes mellitus, the use of glucose-lowering agents or a baseline fasting plasma glucose ≥7 mmol/l and a definitive diagnosis of diabetes during the first year of follow-up. Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) formula. For the classification of renal function we used the eGFR cutoff values as described by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Smoking was self-reported and classified as “current”, “former” and “never”. Physical activity was measured with a previously validated questionnaire and expressed in metabolic equivalent (MET) hours per week, with use of the MET intensities derived from the ‘Compendium of Physical Activity’.

**ABI measurements:**
ABI measurements were conducted by experienced professionals in the vascular lab of the UMC Utrecht, a tertiary referral center for vascular surgery. A Vasoguard dopplerprobe (8MHz) was used to measure the SBP of the bilateral posterior tibial and dorsalis pedis arteries. For each ankle, the highest SBP out of these two was used for the ABI calculations. An average SBP was calculated for each arm from at least 2 measurements of the brachial artery. The arm with the highest average was used for the ABI calculations. The leg-specific ABIs were thus calculated by dividing the highest average arm SBP by the highest of the ankle pressures of that leg. If the ABI could not be obtained due to incompressibility of the artery (> 250 mmHg), this was registered.

**Follow up and outcome ascertainment**
Patients were sent questionnaires biannually, to assess the occurrence of new health outcomes. Reported potential outcomes were checked with health records from treating physicians. All available data were presented to three members of the outcome adjudication committee, who independently classified each outcome. The three classifications were compared and if any disagreement existed, a principal investigator was consulted.

Our primary outcome is a compound of major cardiovascular events, comprising myocardial infarction (MI), stroke, and vascular death. Secondary outcomes are stroke, MI and vascular death separately and all-cause mortality. Vascular death was defined as death from stroke, MI, congestive heart failure, rupture of abdominal aortic aneurysm and vascular death from other causes. Detailed descriptions of outcome definitions are described elsewhere. Participants were followed up until the 1st of March 2013, resulting in a median follow-up of 6.9 years for total mortality and 6.5 years for the compound outcome, with complete follow-up data for 94.5% of participants.

Data analysis

Patients were excluded when they had at least one leg with an ABI ≤0.90 (N= 1376). Patients were counted in the “high ABI” group if they had at least one leg with an ABI ≥ 1.40 or incompressible arteries (N=339). If both legs had ABI values within reference limits (>0.90 and <1.40) patients were placed in the reference group (N=7203). For 36 patients we only had a measurement for one leg available, they were categorized according to the ABI measurement of that leg. Patients with ABI missing for both legs (N=33) were excluded from the analysis. This resulted in a final sample of 7542 patients (Figure 1).

Characteristics of study population across ABI categories were calculated as means with standard deviation or medians with interquartile range (in case of non-normally distributed variables) for continuous variables or percentages with number of cases for categorical variables. Risk factors were compared between patients with high and reference-range ABI using a logistic regression model with high ABI as outcome parameter for each risk factor, adjusted for age and sex, except for the models for age (unadjusted) and sex (adjusted for age). As a sensitivity analysis, the models for non-HDL and SBP were additionally adjusted for lipid-lowering drugs and blood pressure-lowering drugs, respectively, because the proportion treated differed between people with reference range and high ABI.

To assess whether high ABI is associated with an increased risk for the described outcomes when compared to ABI in the reference range, Cox proportional hazards regression was used, with the ABI modeled as a categorical variable (high versus reference range). Crude, sex/age-adjusted and multivariable (sex, age, smoking status, diabetes status, non-HDL cholesterol, SBP, eGFR and prevalent CVD) adjusted models were constructed. As literature suggests that diabetes, high blood pressure and renal function are potentially in the causal pathway leading to arterial calcification or arterial stiffness (and thus high ABI) and CVD 7, we performed analyses with and without these confounders. As a sensitivity analysis, we ran the multivariable model for MI again, this time adjusting for CHD instead of CVD. For the compound outcome a sensitivity analysis excluding all patients with peripheral artery disease (n= 210) was performed. The proportional hazards assumption was checked visually by plotting Schoenfeld residuals; no deviation from proportionality was observed.

Missing values on baseline characteristics that were used in multivariable analyses were filled in using multiple imputation techniques and multivariable analyses were run on m=15 imputed datasets and combined. 8 1.2% or less was originally missing from these imputed variables. As this study used data from an existing cohort, no formal sample size calculation was conducted. Assuming a ratio of high versus non-abnormal ABI of 1:20, a known number of events for the compound endpoint of 694 and a type I error rate of 5%, we had 90% power to detect a HR of 1.6.
To study whether the association of high ABI with CVD is similar among subgroups defined by the presence of diabetes and of prevalent CVD, we ran the final multivariable models for compound CVD and myocardial infarction in the population stratified by these characteristics. We tested for the presence of a significant interaction by adding interaction terms to the multivariable adjusted models for the full population.

All statistical analyses were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria.). Add-on packages ‘Amelia’ (1.7.2) and ‘survival’(2.37-7) were used for multiple imputation and Cox proportional hazards regression, respectively.

**References**


