Common Carotid Intima-Media Thickness Measurements Do Not Improve Cardiovascular Risk Prediction in Individuals With Elevated Blood Pressure

The USE-IMT Collaboration


Abstract—Carotid intima-media thickness (CIMT) is a marker of cardiovascular risk. It is unclear whether measurement of mean common CIMT improves 10-year risk prediction of first-time myocardial infarction or stroke in individuals with elevated blood pressure. We performed an analysis among individuals with elevated blood pressure (ie, a systolic blood pressure ≥140 mmHg and a diastolic blood pressure ≥ 90 mmHg) in USE-IMT, a large ongoing individual participant data meta-analysis. We refitted the risk factors of the Framingham Risk Score on asymptomatic individuals (baseline model) and expanded this model with mean common CIMT (CIMT model) measurements. From both models, 10-year risks to develop a myocardial infarction or stroke were estimated. In individuals with elevated blood pressure, we compared discrimination and calibration of the 2 models and calculated the net reclassification improvement (NRI). We included 17 254 individuals with elevated blood pressure from 16 studies. During a median follow-up of 9.9 years, 2014 first-time myocardial infarctions or strokes occurred. The C-statistics of the baseline and CIMT models were similar (0.73). NRI with the addition of mean common CIMT was small and not significant (1.4%; 95% confidence intervals, −1.1 to 3.7). In those at intermediate risk (n=5008, 10-year absolute risk of 10% to 20%), the NRI was 5.6% (95% confidence intervals, 1.6–10.4). There is no added value of measurement of mean common CIMT in individuals with elevated blood pressure for improving cardiovascular risk prediction. For those at intermediate risk, the addition of mean common CIMT to an existing cardiovascular risk score is small but statistically significant.

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Key Words: atherosclerosis ■ carotid intima-media thickness ■ primary prevention ■ prognosis ■ risk
Hypertension, defined as a blood pressure of 140/90 mm Hg or above, is one of the most important preventable causes of death worldwide. It is a major risk factor for cardiovascular disease (CVD), chronic kidney disease, cognitive decline, and premature death. The risk for these diseases increases gradually with increasing blood pressure levels. Reduction of blood pressure levels through nonpharmacological or pharmacological treatment considerably reduces the risk of CVD.

Target organ damage assessment in patients with hypertension is recommended by international guidelines to define cardiovascular risk beyond traditional risk factors. Carotid intima-media thickness (CIMT) can be considered as a measure of subclinical vascular damage. As such, the 2007 European Society of Hypertension/European Society of Cardiology hypertension guidelines suggests that common CIMT >0.9 mm can be taken as a conservative estimate of existing abnormalities, and that it would make cardiovascular risk stratification in individuals with hypertension more precise. The more recent 2013 ESH/ESC guideline summarizes the existing evidence without any recommendation about the use of CIMT to improve cardiovascular risk prediction.

The existing evidence that CIMT would indeed improve cardiovascular risk prediction in the general population is inconsistent. Whereas there is solid evidence that mean common CIMT does not improve risk stratification on top of Framingham risk score in the general population, the Rotterdam study has shown that common CIMT measurements may be worthwhile in older women. The Atherosclerosis Risk in Communities (ARIC) investigators showed correct reclassification of 9.9% of the general population when plaque information was added to risk precision. Also, the Carotid Intima Media Thickness and IMT-Progression as Predictors of Vascular Events in a High Risk European Population (IMPROVE) study showed that the average of 8 maximal CIMT measurements, alone or combined with interadventitia common carotid artery diameter, classified events and nonevents better than the mean common CIMT. Recently, the Framingham study revealed that the added values in their cohort depended on the site of measurement, IMT of the internal carotid artery was more predictive than that of the common carotid segment.

Given the focus of hypertension guidelines on assessing target organ damage with the goal to determine risk more accurately, we assessed the value of mean common CIMT in individuals with elevated blood pressure. For this objective, we made use of the USE-IMT collaboration, a global individual participant data meta-analysis project based on prospective cohort studies.

Methods

Study Selection

USE-IMT is an ongoing individual participant data meta-analysis, of which the selection of cohorts has been described in detail elsewhere. In short, eligible cohorts were identified through literature searches of databases and through expert suggestion. For the current analyses, 16 cohorts are included, which were required to have available baseline data on age, sex, cigarette smoking status, antihypertensive medication use, diabetes mellitus status, blood pressure, cholesterol levels, common CIMT measurements, history of CVD, and follow-up information on the occurrence of CVD. Individual data from cohorts were collected and harmonized for the statistical analyses using SPSS version 17 (SPSS Inc, Chicago, IL). Given that this is a pooling study of existing data, the study was reviewed by the Institutional Review Board of the University Medical Center, Utrecht. It was decided that the study did not require informed consent from individual patients (who already gave informed consent for the original studies).

Elevated Blood Pressure, Common CIMT, and Outcome

The total USE-IMT cohort represents 56193 individuals, of whom information on mean common CIMT is available and to whom the risk scores apply (individuals are aged 35–74 years, free from previous symptomatic CVD, with total cholesterol level <8 mmol/l, and a systolic blood pressure <180 mm Hg). For the current analysis, we selected 17254 individuals from these 56193 individuals with systolic blood pressure ≥140 mm Hg and a diastolic blood pressure ≥90 mm Hg. The selection was irrespective of the use of blood pressure–lowering drugs. Furthermore, we constructed several subgroups within the population. We considered the added value of mean common CIMT separately for those with diastolic and systolic hypertension. In addition, we also evaluated the added clinical value of mean common CIMT in those with controlled hypertension (normal blood pressure with the use of antihypertensive drugs).

Incomplete data on mean common CIMT, cardiovascular risk factors, and (time to) CVD events, ≈12% of total values, were imputed, as described previously.

Data on reproducibility on CIMT per study have been recently published in the electronic supplementary file. Average mean common CIMT was calculated for each individual using the maximum set of carotid angles, near and far wall measurements, and left and right side measurements that were assessed within each cohort. CIMT measurements from other locations than the common carotid segment were not considered in this analysis. Carotid plaque data were not evaluated because this had not been collected in USE-IMT as a separate variable. However, when a plaque was present in the common carotid segment at the place where the CIMT measurements were taken, it was included in the CIMT measurement and in the analysis. For the analysis on common CIMT of the 90th percentile or above, we created this group separately for every cohort, based on sex and age categories (per 10 years).

The discriminative value of both models was expressed with Harrell C-Index. The 10-year absolute risk to develop a first-time myocardial infarction or stroke was calculated from the model with and without common CIMT.

Individuals with elevated blood pressure were selected and their predicted risks (with either the baseline model or the CIMT model) were used to classify them into a risk category. The following cutoffs were used: <5% (low risk), ≥5% to <10% (low to intermediate risk), ≥10 to <20% (intermediate to high risk), or ≥20% (high risk).

For the subjects with elevated blood pressure, the net reclassification improvement (NRI; taking survival time into account) was calculated using the percentage of correct movement across categories for those with and without events. Correct movement is upward classification by a new marker in those with events and downward classification for those without events.

Because cardiovascular risk may be underestimated in people who are already taking antihypertensive therapy, we performed an additional analysis to determine whether or not mean common CIMT would be useful in improving CVD risk in already treated for hypertension (n=5515). These are the so-called individuals with uncontrolled hypertension (with medication, but still hypertensive).

Statistical Analysis

The original variables of the Framingham risk score (age, sex, and cigarette smoking status, blood pressure, antihypertensive medication use, total cholesterol levels, high-density lipoprotein–cholesterol levels, and presence of diabetes mellitus) were refit on the complete USE-IMT cohort using a multivariable Cox proportional-hazards model. Subsequently, this baseline model was extended with the common CIMT measurement or with the dichotomous variable that indicated who has a CIMT above the 90th percentile.

The discriminative value of both models was expressed with Harrell C-Index. The 10-year absolute risk to develop a first-time myocardial infarction or stroke was calculated from the model with and without common CIMT.
All analyses were performed in the statistical environment R (version 2.10.0). All statistical testing was 2-sided, and a P value of <0.05 was considered statistically significant.

Results

General Characteristics
Table 1 shows the cohorts that were included in this analysis. The total number of individuals with elevated blood pressure in USE-IMT was 17,254, of which 5517 were on blood pressure–lowering medication. The characteristics of the USE-IMT population and population with elevated blood pressure are shown in Table 2. The mean common CIMT (SD) in the subjects with elevated blood pressure 0.79 mm (0.17) compared with 0.74 mm (0.17) in the total USE-IMT population. The age- and sex-adjusted cutoff values for the 90th percentile ranged from 0.83 to 1.15 mm (Table 1). The median follow-up of the individuals with elevated blood pressure was 9.9 years, during which 2014 first-time myocardial infarctions or first-time strokes occurred (Table 2).

Relation Between Common CIMT and First-Time Myocardial Infarction or Stroke
The risk factor relations between the classical cardiovascular risk factors used in the Framingham Risk Score, common CIMT, and the outcome for the general USE-IMT population and the population with elevated blood pressure are displayed in Table 3. Risk factors were strongly related with the occurrence of first-time stroke or myocardial infarction. Yet, among those with elevated blood pressure, blood pressure–lowering medication and diabetes mellitus were less strong predictors for events than in the overall general population. The association between mean common CIMT and outcome was similar (magnitude and direction) for the general USE-IMT population and for the population with elevated blood pressure. The risk factor relations for separate end points are displayed in Tables 4 and 5. Per SD increase with mean common CIMT, the HR for stroke was higher as compared with myocardial infarction.

Calibration
The addition of mean common CIMT improved the baseline model in the whole USE-IMT population (Wald test and the likelihood ratio test, both P<0.001). For the individuals with elevated blood pressure, the 10-year predicted risk was closely in agreement with the 10-year CVD risk as estimated with Kaplan–Meier estimates as given in Figure 1.

Discrimination
The C-statistic for the baseline model was 0.732 (95% confidence intervals [95% CI], 0.721–0.743) and 0.733 (95% CI, 0.722–0.745) for the CIMT model.

Distribution Framingham Risk Score in Individuals With Elevated Blood Pressure
The distribution of the predicted risk, according to the Framingham Risk Score, was as follows: 25.5% was classified as being at low risk (<5%), 33.1% was classified as being at

Table 1. Included Cohort Studies in this Analysis of USE-IMT

<table>
<thead>
<tr>
<th>Name</th>
<th>Acronym or Abbreviation</th>
<th>Location</th>
<th>Number of Individuals With Elevated Blood Pressure (% of total, n=17,254)</th>
<th>Total Number of Participants</th>
<th>90th Percentile of IMT</th>
<th>Number of Events</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis Risk in Communities</td>
<td>ARIC</td>
<td>United States</td>
<td>2351 (14)</td>
<td>14,322</td>
<td>0.83</td>
<td>1192</td>
<td>28</td>
</tr>
<tr>
<td>Carotid Atherosclerosis Progression Study</td>
<td>CAPS</td>
<td>Germany</td>
<td>916 (5)</td>
<td>3885</td>
<td>0.90</td>
<td>128</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular Health Study</td>
<td>CHS</td>
<td>United States</td>
<td>1090 (6)</td>
<td>3121</td>
<td>1.03</td>
<td>712</td>
<td>29</td>
</tr>
<tr>
<td>Malmö Diet and Cancer Study</td>
<td>Malmö</td>
<td>Sweden</td>
<td>2825 (16)</td>
<td>4767</td>
<td>0.94</td>
<td>315</td>
<td>30</td>
</tr>
<tr>
<td>Tromsø Study</td>
<td>Tromsø</td>
<td>Norway</td>
<td>2200 (13)</td>
<td>4242</td>
<td>0.97</td>
<td>558</td>
<td>31</td>
</tr>
<tr>
<td>Multi-ethnic Study of Atherosclerosis</td>
<td>MESA</td>
<td>United States</td>
<td>1313 (8)</td>
<td>5894</td>
<td>0.95</td>
<td>167</td>
<td>32</td>
</tr>
<tr>
<td>Kuopio Ischemic Heart Disease Risk Factor Study</td>
<td>KIHD</td>
<td>Finland</td>
<td>406 (2)</td>
<td>879</td>
<td>0.95</td>
<td>152</td>
<td>33</td>
</tr>
<tr>
<td>Edinburgh Artery Study</td>
<td>EAS</td>
<td>United Kingdom</td>
<td>346 (2)</td>
<td>622</td>
<td>1.00</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td>The Firefighters and Their Endothelium Study</td>
<td>FATE</td>
<td>Canada</td>
<td>438 (3)</td>
<td>1441</td>
<td>0.95</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Charlottesville Study</td>
<td>Charlottesville Study</td>
<td>United States</td>
<td>312 (2)</td>
<td>610</td>
<td>1.03</td>
<td>712</td>
<td>36</td>
</tr>
<tr>
<td>Northern Manhattan Study</td>
<td>NOMAS Study</td>
<td>United States</td>
<td>589 (3)</td>
<td>1093</td>
<td>0.83</td>
<td>57</td>
<td>37</td>
</tr>
<tr>
<td>The Hoorn Study</td>
<td>Hoorn Study</td>
<td>The Netherlands</td>
<td>118 (1)</td>
<td>248</td>
<td>1.04</td>
<td>11</td>
<td>38</td>
</tr>
<tr>
<td>Osaka Follow-Up Study for Carotid Atherosclerosis 2</td>
<td>OSACA2 Study</td>
<td>Japan</td>
<td>182 (1)</td>
<td>403</td>
<td>1.15</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Whitehall II</td>
<td>Whitehall II</td>
<td>United Kingdom</td>
<td>2440 (14)</td>
<td>9748</td>
<td>0.98</td>
<td>257</td>
<td>40</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>Rotterdam</td>
<td>The Netherlands</td>
<td>1433 (8)</td>
<td>3718</td>
<td>0.92</td>
<td>642</td>
<td>41</td>
</tr>
<tr>
<td>Non-Invasive measurements of Atherosclerosis in the Nijmegen Biomedical Study</td>
<td>NIMA-NBS</td>
<td>The Netherlands</td>
<td>295 (2)</td>
<td>1200</td>
<td>0.97</td>
<td>17</td>
<td>42,43</td>
</tr>
</tbody>
</table>
Table 2. Characteristics of the Population With Elevated Blood Pressure and of the USE-IMT Population

<table>
<thead>
<tr>
<th>Baseline and Follow-Up Information</th>
<th>Elevated Blood Pressure Group (n=17254)</th>
<th>USE-IMT (n=56193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>61 (45–75)</td>
<td>59 (45–75)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg (SD)</td>
<td>150 (12.2)</td>
<td>129 (18.8)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg (SD)</td>
<td>86 (10.8)</td>
<td>76 (10.8)</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>18%</td>
<td>20%</td>
</tr>
<tr>
<td>Blood pressure–lowering medication, %</td>
<td>32%</td>
<td>23%</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L (SD)</td>
<td>5.9 (1.02)</td>
<td>5.7 (1.02)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L (SD)</td>
<td>1.4 (0.42)</td>
<td>1.4 (0.43)</td>
</tr>
<tr>
<td>Common CIMT, mm</td>
<td>0.79 (0.171)</td>
<td>0.74 (0.165)</td>
</tr>
<tr>
<td>Framingham 10-year risk % (SD)</td>
<td>11 (8.7)</td>
<td>7.0 (6.8)</td>
</tr>
<tr>
<td>Follow-up, median (IQR), y</td>
<td>9.9 (6.4–11.8)</td>
<td>9.5 (6.4–12.6)</td>
</tr>
<tr>
<td>No. of myocardial infarctions</td>
<td>1090</td>
<td>2454</td>
</tr>
<tr>
<td>No. of strokes</td>
<td>1074</td>
<td>2104</td>
</tr>
<tr>
<td>No. of first-time myocardial infarction or stroke</td>
<td>2014</td>
<td>4290</td>
</tr>
</tbody>
</table>

CIMT indicates carotid intima-media thickness; HDL, high-density cholesterol; IQR, interquartile range; and USE-IMT, •••.

low to intermediate risk, (≥5 to <10%), 29.0% was classified as being at intermediate to high-risk, (≥10 to <20%), and 12.4% was classified as being at high risk (≥20%). Women had an overall lower CVD risk, and the distribution of women across the risk categories was as follows: 34% was classified as being at low risk, 35% was classified as being at low to intermediate risk, 24% was classified as being at intermediate to high risk, and 7% was classified as being at high risk. For men, the classification was 18% at low risk, 32% at low to intermediate risk, 33% as intermediate to high risk, and 17% at high risk.

NRI in Individuals With Elevated Blood Pressure

The upper part of Figure 2 shows the distribution of the number of individuals without and with events across risk categories based on the Framingham Risk Score (rows), and the distribution of individuals with and without events after the addition of the common CIMT (columns). The percentage of individuals that remained in the same risk category was high (>85%). The observed mean risk (lower part of Figure 2) of the individuals that remained in the same risk categories (gray) corresponded well with the risk categories. There was a similar number of individuals without events correctly classified to a lower risk category (sum of 412, 445, and 186 individuals) as incorrectly classified to a higher risk category (sum of 312, 398, and 178 individuals) as shown in the top table of Figure 2. In addition, there was a similar number of individuals with events correctly classified to a higher risk category (sum of 20, 50, and 56 individuals) as incorrectly classified to a lower risk category (sum of 22, 60, and 49 individuals). In the lower part of Figure 2, the observed risks in those who shifted risk category show much uncertainty, as indicated by the wide upper and lower limits of the Kaplan–Meier estimates. As a result, the calculated NRI indicated that the added value of common CIMT was small and nonsignificant (1.4%; 95% CI [−1.1 to 3.7]). Results for men were 0.7% (95% CI [−0.2 to 0.4]) and for women 2.9% (95% CI [−0.2 to 5.4]). In those at intermediate risk (10% to 20%), the NRI was 5.6% (95% CI [1.6–10.4]) with no differences between men and women. When using a cutoff point for common CIMT of the 90th percentile or above, the NRIs were similar to that reported above (overall NRI was 1.4%, 95% CI, −0.3 to 3.9; for the intermediate group: 5.0%, 95% CI, 1.3–7.6). When 3 categories were applied merging the 2 middle intermediate risk categories to 1 from 5% to 20% risk, the NRI was 0.9% (95% CI [−0.2 to 0.4]) and for women 2.9% (95% CI [−0.2 to 5.4]). For the intermediate group, the NRI was 5.1% (95% CI, 3.2–7.8).

NRI in Individuals With Elevated Blood Pressure on Blood Pressure–Lowering Drugs

In those treated for hypertension (n=5517), the average systolic blood pressure (SD) was 151 (12.4) mmHg, and the average diastolic blood pressure was 86 (11.4) mmHg. Mean common CIMT was 0.81 mm. The median follow-up in this group was 8.5 years, during which 676 first-time myocardial infarction and

Table 3. Relation Between Risk Factors With Cardiovascular Events in the Subset of Individuals With Elevated Blood Pressure and in All Participants of USE-IMT

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>USE-IMT (n=56193)</th>
<th>Individuals With Elevated Blood Pressure (n=17254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td></td>
</tr>
<tr>
<td>Age, per SD increase (SD=8.4 y)</td>
<td>1.60 (1.53–1.68)</td>
<td>1.55 (1.45–1.66)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.94 (1.78–2.11)</td>
<td>1.75 (1.54–1.98)</td>
</tr>
<tr>
<td>Treatment for high blood pressure, yes vs no</td>
<td>1.32 (1.23–1.41)</td>
<td>1.17 (1.06–1.29)</td>
</tr>
<tr>
<td>Sex, male vs female</td>
<td>1.50 (1.40–1.61)</td>
<td>1.46 (1.32–1.61)</td>
</tr>
<tr>
<td>HDL-cholesterol, per SD increase (SD=0.43 mmol/l)</td>
<td>0.62 (0.59–0.65)</td>
<td>0.64 (0.61–0.67)</td>
</tr>
<tr>
<td>Common CIMT, per increase of 1 SD (SD=0.16 mm)</td>
<td>1.15 (1.12–1.18)</td>
<td>1.13 (1.09–1.18)</td>
</tr>
<tr>
<td>Systolic blood pressure, per SD mmHg increase (SD=19 mmHg)</td>
<td>1.32 (1.28–1.37)</td>
<td>1.35 (1.25–1.44)</td>
</tr>
<tr>
<td>Current cigarette smoking, yes vs no</td>
<td>1.70 (1.59–1.83)</td>
<td>1.65 (1.49–1.82)</td>
</tr>
<tr>
<td>Total cholesterol, per SD</td>
<td>1.12 (1.08–1.16)</td>
<td>1.08 (1.03–1.14)</td>
</tr>
</tbody>
</table>

CIMT indicates carotid intima-media thickness; HDL, high-density cholesterol; and USE-IMT, •••.
strokes occurred. In these individuals, the C-statistic without CIMT was 0.726 (95% CI, 0.706–0.746) and 0.730 (95% CI, 0.711–0.750) with the addition of mean common CIMT. The clinical added value of mean common CIMT to the Framingham Risk Score in terms of NRI was 2.7% (95% CI, −1.9 to 6.6). For the intermediate risk group (10–20% absolute 10-year risk for first-time myocardial infarction and stroke), the NRI was 7.7% (95% CI, 0.5 to 15.1) after the addition of mean common CIMT.

NRI in Individuals With Controlled Elevated Blood Pressure

In the 7688 individuals with controlled elevated blood pressure, mean common CIMT was 0.75 mm. The median follow-up was 9 years, during which 677 first-time myocardial infarction and strokes occurred. The NRI after addition of mean common CIMT to Framingham Risk Score in terms of NRI was 2.1% for all individuals with controlled hypertension; for the intermediate group (10–20% absolute 10-year risk for first-time myocardial infarction and stroke), the NRI was 7.3%.

NRI in Individuals With Systolic and Diastolic Hypertension

When studying the added value of mean common CIMT in individuals with systolic and diastolic hypertension separately, we observed that there were 15,552 individuals with systolic hypertension (systolic blood pressure ≥140 mm Hg) and 7449 individuals with diastolic hypertension (diastolic blood pressure ≥90 mm Hg). The median follow-up in these groups was 9.1 years and 9.3 years, leading to 1020 and 464 first-time events, respectively. The addition of mean common CIMT to Framingham Risk Score resulted in an NRI of 1.4% in persons with systolic hypertension and an NRI of 1.2% in persons with diastolic hypertension.

Analysis of the End Point Myocardial Infarction and Stroke Separately

Tables 4 and 5 display the risk factor relations for the separate end point myocardial infarction and stroke. In the entire USE-IMT cohort, there were 2104 strokes and 2454

<table>
<thead>
<tr>
<th>Table 4. Relation Between Risk Factors and Stroke in the Subset of Individuals With Elevated Blood Pressure and in All Participants of USE-IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age, per SD increase (SD=8.4 y)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Treatment for high blood pressure, yes vs no</td>
</tr>
<tr>
<td>Sex, male vs female</td>
</tr>
<tr>
<td>HDL-cholesterol, per SD increase (SD=0.43 mmol/l)</td>
</tr>
<tr>
<td>Systolic blood pressure, per SD mm Hg increase (SD=19 mm Hg)</td>
</tr>
<tr>
<td>Current cigarette smoking, yes vs no</td>
</tr>
<tr>
<td>Total cholesterol, per SD</td>
</tr>
<tr>
<td>Common CIMT, per increase of 1 SD (SD=0.16 mm)</td>
</tr>
</tbody>
</table>

CIMT indicates carotid intima-media thickness; HDL, high-density cholesterol; and USE-IMT, •••.

<table>
<thead>
<tr>
<th>Table 5. Relation Between Risk Factors and Myocardial Infarction in the Subset of Individuals With Elevated Blood Pressure and in All Participants of USE-IMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age, per SD increase (SD=8.4 y)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Treatment for high blood pressure, yes vs no</td>
</tr>
<tr>
<td>Sex, male vs female</td>
</tr>
<tr>
<td>HDL-cholesterol, per SD increase (SD=0.43 mmol/l)</td>
</tr>
<tr>
<td>Systolic blood pressure, per SD mm Hg increase (SD=19 mm Hg)</td>
</tr>
<tr>
<td>Current cigarette smoking, yes vs no</td>
</tr>
<tr>
<td>Total cholesterol, per SD</td>
</tr>
<tr>
<td>Common CIMT, per increase of 1 SD (SD=0.16 mm)</td>
</tr>
</tbody>
</table>

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myocardial infarctions. The included patients with elevated blood pressure (irrespective of blood pressure medication) experienced 1074 strokes and 1090 myocardial infarctions. The NRI for stroke was 2.7%, and the NRI for myocardial infarction was 0.7%.

Discussion

In the present analysis, we observed no additional value of measurement of mean common CIMT in risk classification among 17254 individuals free from symptomatic CVD, but with elevated blood pressure levels. For those at intermediate risk, the addition of common CIMT to an existing cardiovascular risk score is small but statistically significant. However, the decision on whether or not to implement common CIMT measurements in individuals with elevated blood pressure levels at intermediate risk depends on the balance between costs of additional risk assessment by CIMT measurements and effectiveness in preventing CVD.

In asymptomatic individuals with elevated blood pressure, guidelines recommend cardiovascular risk assessment and suggest screening for subclinical vascular damage. It has been suggested that providing a more accurate assessment of vascular damage related to hypertension may lead to a more precise stratification of CVD risk. As such, the 2007 ESH/ESC hypertension guidelines suggested that ultrasound scanning may be useful to detect vascular damage in individuals with hypertension; however, the more recent 2013 guideline is already cautious in their advice. Our results may add to the body of evidence that mean common CIMT measurements are not useful to improve CVD risk assessment in those with elevated blood pressure.

Elevated blood pressure is one of the factors that promotes atherosclerosis. In our population of individuals with elevated blood pressure, common CIMT was indeed thicker compared with the general population in USE-IMT. Also, the average Framingham absolute 10-year risk for CVD/myocardial infarction and stroke was 11% as compared with 7% of the total USE-IMT population. Most studies that addressed the added value of common CIMT measurements in CVD risk prediction have been based on the general population or specific high-risk populations. These studies pointed toward an added value of presence of plaque and CIMT in the bifurcation and internal carotid artery for improving CVD risk. Recent data from the Framingham and the IMPROVE studies indicate that a combination of ultrasound measurements of several carotid segments in addition to the presence of plaques may be clinically more useful in reclassifying individuals to correct risk categories than measurement in the common carotid artery alone. Also, in those with hypertension, a recent study indicates that plaque score is a better predictor for the onset of stroke than mean CIMT. Because information on carotid plaque was not available in USE-IMT, we can only draw conclusions on the predictive value of mean common CIMT. Even our findings with a dichotomous value greater than the 90th percentile for common CIMT did not help in risk stratification. Future research should be directed toward assessing whether CIMT and plaque information from other sites than the common carotid may be useful in CVD risk classification.

Our findings expand the evidence by showing that mean common CIMT may not be useful in clinical practice to improve individual 10-year risk prediction in a population with elevated blood pressure. Hence, our results may help to update the present guidelines on their advice not to use mean common CIMT measurements for risk classification among individuals with elevated blood pressure. Because further discrimination of the intermediate risk group into either high risk (requiring more aggressive treatment) and low risk (management with lifestyle intervention alone) is desirable, we specifically addressed this group in our analysis. This analysis showed a small improvement in risk prediction in the intermediate risk group, as was previously reported in the intermediate risk group in the whole USE-IMT population. Final conclusions on the value of using common CIMT measurements in clinical practice should be based on the balance between additional risk assessment by CIMT measurements and effectiveness in preventing additional cardiovascular events. Recently, such cost-effectiveness analysis was published using data from the ARIC study, where, in the whole population, the combination of common CIMT and carotid plaque information yielded an NRI of 9.9%. The cost-effectiveness analyses indicated that performing these common CIMT and carotid plaque measurements in asymptomatic men and women aged 50 to 59 years results in small and cost-effective health benefits, in particular in women. However, because the NRI estimates in individuals with elevated blood pressure levels observed in the present study were smaller than those observed in ARIC, cost-effectiveness is less likely to be achieved.
USE-IMT is today’s largest and most representative individual participant data meta-analysis on the added value of CIMT in the prediction of cardiovascular events. A limitation that we cannot account for is the variation in CIMT measurements across studies. In this analysis, we therefore created a dichotomous variable that indicates who exceeds the 90th percentile CIMT per sex and age category, separately for every study. This may have removed some of the study-specific variation. Because the results of this 90th percentile CIMT were exactly similar to that of the linear mean common CIMT results, we are confident that our conclusion is valid. Also, the use of a Frailty model in our Cox proportional-hazards model corrected for the differences in CIMT and outcome across studies. Another limitation of USE-IMT is that not all relevant cardiovascular end points are available in the cohorts. For example, cardiovascular mortality, all-cause mortality, transient ischemic attack, and angina pectoris were only available in a limited number of cohorts. To limit any selection bias, analyses for other end points than myocardial infarction and stroke were therefore not performed. Also, there are many more cardiovascular risk prediction scores available,26 also for individuals with hypertension separately.27 Yet, many contain variables that are currently unavailable within USE-IMT such as presence of left ventricular hypertrophy and creatinin. Therefore, our results on the limited added value mean common CIMT apply only to Framingham Risk Score.

Perspectives
There is no added value of measurement of mean common CIMT in individuals with elevated blood pressure in cardiovascular risk prediction. For those at intermediate risk, the addition of common CIMT to an existing cardiovascular risk score is small but statistically significant. The ultimate decision to implement use of common CIMT measurements in the intermediate group with elevated blood pressure depends on the balance between costs and effectiveness, that is, lives saved, events prevented, and quality adjusted life-years gained.

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Disclosures
None.

References


**Novelty and Significance**

**What Is New?**
- Measuring mean common carotid intima-media thickness (CIMT) does not add to Framingham risk stratification in individuals with elevated blood pressure and without symptomatic cardiovascular disease.
- Measuring mean common CIMT slightly improves cardiovascular risk prediction for those already classified as intermediate risk.

**What Is Relevant?**
- Many primary care physicians are uncertain whether or not to perform a CIMT measure in those with elevated blood pressure to improve cardiovascular risk prediction. Our study provides scientific evidence to guide primary care physicians on CIMT measures in this population.

**Summary**
There is no added value of measurement of common CIMT in individuals with elevated blood pressure for improving cardiovascular risk prediction. Primary care physicians are not recommended to use common CIMT to improve risk prediction in this population.
Common Carotid Intima-Media Thickness Measurements Do Not Improve Cardiovascular Risk Prediction in Individuals With Elevated Blood Pressure: The USE-IMT Collaboration


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Karlijn A. Groenewegen: Analysis of the data, drafting of the manuscript and critical revision of the manuscript

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