Carotid Intima-Media Thickness as a Marker of Cardiovascular Risk in Hypertensive Patients With Coronary Artery Disease

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Background: The aim of this study was to examine the significance of ultrasound-measured carotid intima-media thickness (CIMT) in high-risk patients with hypertension and coronary artery disease (CAD), as an independent prognostic factor in determining the risk of all-cause death or future cardiovascular events.

Methods: The study included 297 consecutive patients (mean age ± SD, 57 ± 9.4 years) with diagnosed hypertension and CAD, referred for coronary angiography. The mean of maximal CIMT in two arterial segments bilaterally was calculated. The primary endpoint was a patient’s death from all causes. Death, stroke, or myocardial infarction comprised the secondary, composite endpoint.

Results: There was a follow-up of 1 to 79 (mean, 41) months. The predictors of death in a multivariate Cox proportional hazards model were the number of stenosed coronary arteries ($P = .007$) and CIMT ($P = .001$). The risk of the secondary, composite endpoint (death, stroke, or myocardial infarction) was determined by diabetes ($P = .008$) and CIMT ($P = .100$). Nearly 99% of patients with “low CIMT” ($\leq 1.13$ mm) survived for 5 years, versus 78% with “high CIMT” (>1.13 mm) (log-rank test; $P < .001$). For the secondary, composite endpoint (death, stroke, or myocardial infarction), the event-free survival rate was 95% (low CIMT), versus 74% after 5 years (high CIMT) ($P < .008$).

Conclusions: Intima-media thickness of the carotid arteries is a strong and independent predictor of death and serious cardiovascular events in hypertensive patients with CAD referred for coronary angiography.

Key Words: Carotid intima-media thickness, prognosis, hypertension, coronary artery disease.

Numerous studies indicate that carotid intima-media thickness (CIMT) with the presence of plaque, as evidenced by ultrasound, is a strong predictor of future cardiovascular events. Pignoli et al established that the distance measured between two lines separated by a hypoechoic space visible in an ultrasound image of the carotid distal wall correlated with the thickness of the intima-media (IMT) layers of the artery measured in vitro and in vivo.¹ Later studies extended this measurement to the thickness of the focal carotid plaque, and this “composite thickness” was used as a marker of atherosclerotic burden.² This method has been widely used since its introduction, and validated in many cross-sectional and longitudinal epidemiologic and clinical studies. Akosah et al showed that carotid atherosclerosis (IMT $\geq 1.0$ mm) was associated with severe coronary disease (odds ratio, 2.2; 95% confidence interval, 1.2 to 4.0) in subjects undergoing elective coronary angiography.³

According to data published after the completion of such major epidemiologic studies as the North American
Cardiovascular Health Study, the Atherosclerosis Risk in Communities (ARIC) Study, the European British Heart Study, and the Rotterdam Study, the increase in intima-media thickness not only correlates with most of the known atherosclerotic risk factors such as systolic hypertension, total and LDL cholesterol levels, cigarette smoking, high-sensitivity C-reactive protein (hsCRP) levels, diabetes, and others, but also increases the risk of cardiovascular events.

The results of the ARIC Study show that with an increase of 0.19 mm of the IMT, the risk of coronary disease increases by 69% in women and 36% in men. The risk of stroke is 8.5 times higher for women and 3.6 times higher for men with IMT ≥1 mm, compared with those with IMT <0.6 mm.

In classic screening procedures, there is a strong tendency to concentrate on modifiable risk factors, especially when the data collection is relatively simple and easily available (eg, blood samples or blood-pressure measurements). However, when patients are treated actively, those classic risk factors can lose their predictive value. The aim of this study was to examine the significance of ultrasound-measured CIMT in high-risk patients with hypertension and coronary artery disease (CAD), as an independent prognostic factor in determining the risk of all-cause death or future cardiovascular events.

Methods

The study group consisted of 279 consecutive patients (mean age ± SD, 57 ± 9.7 years; range, 31 to 82 years) with essential hypertension and a diagnosis of coronary artery disease (CAD) who simultaneously underwent coronary and renal angiography. A history of CAD, type 2 diabetes mellitus, and dyslipidemia, and smoking status and other CAD risk factors, were evaluated.

All subjects underwent a clinical examination. Blood samples from patients for all biochemical evaluations were taken after an overnight fast. Concentrations of lipids, glucose, creatinine, creatinine clearance, uric acid, homocysteine, fibrinogen, and hsCRP were measured using standard laboratory techniques. Characteristics of the patients studied are presented in Table 1.

A significant stenosis of the coronary artery was diagnosed when the degree of stenosis was ≥50% of the vessel diameter. According to the number of stenotic vessels, patients were divided into three groups: those with no significant stenosis or one stenosed artery, those with two stenosed arteries, and those with ≥3 stenosed arteries (or left main stenosis).

Carotid ultrasound, followed by a duplex color Doppler examination, was performed with patients in supine position, with a Phillips ATL 5000 (ATL Poland, Warsaw, Poland) and a linear probe of 7.5 to 12 MHz. Both left and right common carotid arteries were analyzed. Multiple measurements of the distal wall from anterior, lateral, and posterior longitudinal projections were recorded. Maximal IMT was measured in two segments, of 1 cm each, from the flow divider caudally (carotid bulb), and from the beginning of the common carotid bulb (common carotid). The IMT value was calculated as an arithmetical mean from the bulb and common carotid segments of both sides. A median value of 1.13 mm was used for stratification of patients into “high” and “low” CIMT groups.

Lipid disorders were defined as the presence of active pharmacologic antilipemic treatment or plasma levels >200 mg/dL of total cholesterol, or 130 mg/dL of LDL cholesterol, or HDL cholesterol level <35 mg/dL, or a triglycerides plasma level >135 mg/dL. All patients were treated on the basis of their clinical status and angiographic and laboratory findings, according to the judgment of the physician responsible.

An effort was made to contact all patients after their discharge from the hospital. Information obtained from patients and from medical records was analyzed when available. Stroke was diagnosed when a neurologic deficit lasted...
at least 48 h. Myocardial infarction was diagnosed according
to the European Society of Cardiology (ESC) criteria ST
segment elevation myocardial infarction [STEMI] or non-ST
segment elevation myocardial infarction [NSTEMI]. Data on
the survival of patients who had not been contacted directly
were checked in the Polish National Death Registry.

The main endpoint of the study was death from all causes.
The secondary, composite endpoint was myocardial infarc-
tion or stroke or death from all causes. The protocol of the
study was approved by the local ethics committee, and pa-
tients gave informed consent to participate in the study.
A statistical analysis was performed with SPSS version
15.0 software (SPSS Polska Sp. zoo, Krakow, Poland).
The differences between continuous variables between
groups were assessed by ANOVA. A univariate Cox anal-
ysis was performed to determine the influence of variables
analyzed on the defined endpoint. Variables which were
significant in the univariate Cox analysis were included in
the multivariate Cox model. Event-free Kaplan-Meier sur-
vival curves were analyzed. The statistical significance of
event-free survival between groups, divided in terms of the
median IMT values, was assessed with a log-rank test.
Differences were considered statistically significant when
$P < .05$.

**Results**

Follow-up data concerning the survival rate were obtained
for all 297 patients, and data concerning cardiovascular
events were obtained for 97% (288 patients). There was a
mean follow-up period of 41 months (range, 1 to 79 months).

During follow-up, 15 patients (5%) died. The second-
ary, composite endpoint (death from all causes, stroke, or
myocardial infarction) was observed in 27 patients. Pa-
tients who met the primary endpoint (death from all
causes) were characterized by higher age, higher hsCRP
levels, presence of diabetes, higher number of stenosed
coronary vessels, greater CIMT, lower left-ventricular
ejection fraction (LVEF), presence of renal arteries steno-
sis, higher plasma creatinine level, and higher frequency
of diuretic but not statin use.

The analysis using a Cox proportional hazards regres-
sion model was performed and included age, sex, cigarette
smoking, hsCRP level, presence of lipid disorders, diabe-
tes, diuretic use, number of stenosed coronary vessels,
CIMT, LVEF, systolic blood pressure, presence of renal
arteries stenosis, and plasma creatinine levels.

The independent prognostic value in the multivariate
Cox model was found to be significant only for the number
of stenosed coronary vessels ($P < .007$) and the IMT of
carotid arteries ($P < .001$) (Table 2). There was a signif-
icant relation between the number of the stenosed coro-
nary vessels and the CIMT ($P < .001$). Patients with no
significant coronary artery stenosis had a CIMT (mean
SD) of 1.05 ± 0.31 mm; with a one-vessel stenosis, 1.16 ± 0.41
mm; with two-vessel stenoses, 1.32 ± 0.44
mm; and with three-vessel stenoses, 1.28 ± 0.33 mm.

The same set of variables was used for the composite,
secondary endpoint. Statistically significant parameters in
the univariate analysis included age, hsCRP level, pres-
ence of diabetes, diuretic use, number of stenosed coronary
vessels, CIMT, LVEF, systolic blood pressure, presence of renal
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ence of diabetes, diuretic use, number of stenosed coronary
vessels, CIMT, and LVEF. In the multivariate
proportional hazards Cox model, only diabetes ($P < .008$)
and carotid IMT ($P < .010$) were found to have an
independent prognostic value (Table 3).

The survival curve for the primary endpoint is shown in
Fig. 1. The two groups of patients, one with IMT values
≤1.13 mm, and the other with values >1.13 mm, differed
significantly in their survival rate. Nearly 99% of patients

**Table 2.** Primary endpoint: death from all causes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate cox model</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimated odds ratio</td>
<td>95% Confidence interval</td>
</tr>
<tr>
<td></td>
<td>(Exp (B))</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.00–1.13</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td></td>
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<tr>
<td>Cigarette smoking</td>
<td>NS</td>
<td></td>
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<tr>
<td>High-sensitivity C-reactive protein</td>
<td>1.22</td>
<td>1.07–1.40</td>
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<td>Lipid disorders</td>
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</tr>
<tr>
<td>Diabetes</td>
<td>6.66</td>
<td>2.4–18.5</td>
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<tr>
<td>Diuretic use</td>
<td>NS</td>
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<tr>
<td>Number of stenosed coronary vessels</td>
<td>2.27</td>
<td>1.19–4.30</td>
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<tr>
<td>Intima-media thickness of carotid arteries</td>
<td>1.29</td>
<td>1.15–1.44</td>
</tr>
<tr>
<td>Left-ventricular ejection fraction</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Stenosis of renal artery</td>
<td>4.98</td>
<td>1.77–14.00</td>
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<tr>
<td>Plasma creatinine level</td>
<td>1.11</td>
<td>1.01–1.21</td>
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</table>
with low CIMT survived 60 months, versus 78% in the high CIMT group. Differences were statistically significant in the log-rank test ($P < .001$) (Fig. 1).

The survival curve for the secondary, composite endpoint (death, stroke, and myocardial infarction) is shown in Fig. 2. The event-free survival for patients with IMT $\leq 1.13$ mm was 99% for the period of up to 20 months, and 95% for 70 months. Patients with a carotid IMT $>1.13$ mm had an event-free survival rate of 95% for 20 months, but only 74% after 60 months. Differences were statistically significant in the log-rank test ($P < .008$) (Fig. 2).

**Discussion**

Patients who participated in our study were selected from hospitalized, consecutive patients with essential hypertension and clinical symptoms of CAD, who were referred for coronary angiography. This group of patients differed from those included in most epidemiologic studies that described the relationship between IMT and cardiovascular risk in the general population. Our group was characterized by a higher prevalence of risk factors for cardiovascular events, including hypertension and a higher incidence of CAD. On the other hand, these patients were treated more intensively for their known risk factors (eg, hypertension, dyslipidemia, diet, and antismoking counseling), and had a higher motivation for treatment due to the presence of symptoms. The effects of treatment are clearly visible when the baseline data of total cholesterol

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### Table 3. Composite, secondary endpoint: death from all causes, stroke, or myocardial infarction

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Multivariate Cox model</th>
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<tr>
<td></td>
<td>Estimated odds ratio (Exp (B))</td>
<td>95% Confidence interval</td>
</tr>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.02–1.10</td>
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<td>Sex</td>
<td>NS</td>
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<tr>
<td>Cigarette smoking</td>
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<td>High-sensitivity C-reactive protein level</td>
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<td>1.04–1.25</td>
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<tr>
<td>Lipid disorders</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.15</td>
<td>1.89–9.10</td>
</tr>
<tr>
<td>Diuretics</td>
<td>2.74</td>
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<td>Number of stenosed coronary vessels</td>
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<td>1.02–2.11</td>
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<tr>
<td>Intima-media thickness of carotid arteries</td>
<td>1.18</td>
<td>1.08–1.29</td>
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<tr>
<td>Left-ventricular ejection fraction</td>
<td>0.96</td>
<td>0.92–0.99</td>
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<tr>
<td>Systolic blood pressure</td>
<td>NS</td>
<td></td>
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<tr>
<td>Stenosis of renal artery</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Plasma creatinine level</td>
<td>NS</td>
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</tbody>
</table>

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**FIG. 1** Primary endpoint (death from all causes): Kaplan-Meier curves, event-free survival in months. Groups were divided according to intima-media thickness (IMT) values $>1.13$ mm or $\leq 1.13$ mm.

**FIG. 2** Secondary, composite endpoint (death, stroke, or myocardial infarction): Kaplan-Meier curves, event-free survival in months. Groups were divided according to intima-media thickness (IMT) values $>1.13$ mm or $\leq 1.13$ mm.
(mean level 191 mg/dL) or LDL cholesterol (mean level 114 mg/dL) in the study are compared with general-population levels of total cholesterol in the same urban area, ie, 231 mg/dL. The mean value of systolic blood pressure (137 mm Hg) indicates relatively well-controlled hypertension. Patients’ data in our study reflect only the current level of risk factors, biased by active treatment. The historic data of these patients’ risk-factor levels are seldom available and often unreliable.

Ultrasound measurement of the intima-media complex offers the possibility of direct visualization of the presence of atherosclerotic plaque in the carotid arteries. The correlation between IMT and classic risk factors is well-established. Measurement of the intima-media for the purpose of cardiovascular risk assessment in the general population was validated by many epidemiologic studies. However, some studies questioned the additional benefit of this method when added to the classic risk-factor assessment in screening procedures. Because of availability and cost considerations, the ultrasound IMT measurement was not widely recommended as a screening tool to be used in a general population. Its role, however, was recognized as an additional recommended examination by some international and national hypertension societies in guidelines dealing with risk assessment and target-organ involvement in hypertensive disease.

There is ongoing discussion about the potential use of IMT as a tool to predict significant coronary artery stenoses. Adams et al found only a weak correlation between IMT of the common carotid arteries and the severity of CAD. However, many other studies, eg, by Craven et al, Hulthe et al, and Kotis et al, (as well as our own data) found a significant correlation between IMT and the extent of CAD, especially expressed as the number of stenosed coronary vessels.

The data presented here confirm that IMT is a strong predictor of cardiovascular events in patients with hypertension and CAD, among other predictors such as number of stenosed coronary vessels, decreased LVEF, and presence of diabetes included in the Cox proportional hazards model. This independent significance of IMT in predicting cardiovascular events holds true for a definite endpoint such as death by all causes, but also for a composite endpoint (death by all causes, myocardial infarction, or stroke).

The value of IMT as an independent, significant parameter in both analyzed models with different endpoints in our high-risk group of actively treated patients suggests that we should reconsider the possibility of using this method more often for cardiovascular risk stratification in secondary prevention. The “target-organ damage” which resulted in the formation of large atheromatic plaques in the carotid arteries is a slow-reacting marker of atherosclerotic risk. Even when blood pressure and cholesterol levels are nearly normalized by active treatment, plaque and increased IMT are still present. However, atherosclerotic changes take years, and not months, to become visible, and they show a cumulative risk for the individual patient, rather than a fluctuation in the level of one parameter.

For many years, measurement of IMT was approved by regulatory agencies as a surrogate endpoint to assess the effectiveness of drugs’ antiatherosclerotic effects. The variability of measurements systematically decreased, and is now below 10–15%. However, longer-term problems with standardization of the measurement between centers, and the time-consuming procedure of offline measurement, slowed the transition of this method from scientific investigation to clinical practice. We used a simplified online method of measurement of the far wall of the two segments of carotids: the common carotid bulb and the distal part of the common carotid artery, with calculation of maximal IMT in the observed segment within multiple projections, ie, anterior, lateral, and posterior. This allowed us to obtain a better approximation of the spatial distribution of IMT.

Newer imaging techniques using ultrasound with integrated backscatter and magnetic resonance imaging or multislice computed tomography can directly visualize atherosclerotic changes in the arterial tree, and give additional information about plaque (lipid core, calcified, or ulcerated). The calcium score index of coronary arteries was most widely tested as a stratification tool. The use of these new methods is still rare. They are not widely available, and remain rather very expensive.

An increasing role of “new inflammatory” markers, especially hsCRP, for purposes of risk stratification in ischemic artery disease, and the approach to atherosclerotic changes as a dynamic process (the vulnerable plaque hypothesis), reinforce the role of direct visualization techniques to stratify patients at high risk. There is still doubt whether changes in the carotid arteries reflect changes in other vascular beds. The analysis of femoral-artery IMT may give better information. One may also consider analyzing the two locations together. The results of our work indicate that a relatively simple method of IMT measurement, bilaterally only on two segments of the carotid arteries, gives sufficient information for stratification purposes in hypertensive patients with CAD. Patients with multiple coronary-artery stenoses had higher values of CIMT. This correlation probably reflects a more widespread and advanced atherosclerotic process, and possibly individual susceptibility to atherosclerosis, through long-standing endothelial dysfunction and other factors that increase the risk of cardiovascular death. Despite this common pathway of atheromatic plaque formation, both the number of stenosed coronary vessels and CIMT independently influenced the prognosis in a multivariate Cox analysis. The baseline values of LDL cholesterol and statin use did not differ significantly in our group of patients with or without primary endpoints during follow-up.

There are some obvious limitations to our study. The number of patients was <300. They were consecutive patients referred for coronary angiography, and they did not
represent a random sample of hypertensive patients with CAD. Moreover, only a medium follow-up period (mean 41 months) was possible. We did not analyze the degree of left-ventricular hypertrophy, an important marker of survival which is significantly correlated with CIMT and survival, even in a low-risk population. It should also be taken into account that the cutoff value of carotid IMT at \( >1.13 \) mm cannot be directly compared to the values presented by other authors because of methodological differences in methods of measurement.

Despite these limitations, the present method of measuring IMT thickness can differentiate patients with a high and low risk of death, even within such a brief follow-up. The survival rate was nearly 99% in patients with a measured mean maximal IMT \( =1.13 \) mm, as opposed to only 78% in patients with a mean maximal IMT \( >1.13 \) mm. The difference proved to be highly significant, even within such a brief follow-up.

The use of IMT ultrasound measurement visualizes the long-term effects of different risk factors on the arterial wall and on the development of atherosclerotic changes in a given patient. It allows the presence of atherosclerosis to be detected almost directly and, to some extent, semiquantitatively. Due to slow changes, CIMT demonstrates the “overall atherosclerotic burden” and reflects the risk of death and of other cardiovascular events, even when classic risk factors are successfully corrected by therapeutic interventions.

**Conclusions**

Intima-media thickness of the carotid arteries is a strong and independent predictor of serious cardiovascular events: death, stroke, or myocardial infarction in hypertensive patients with CAD referred for coronary angiography in medium-term follow-up.

**References**


**AJH—October 2007—VOL. 20, NO. 10**

**CAROTID IMT AND RISK ASSESSMENT**

**1063**


