ORIGINAL ARTICLE

Prospective study on the prognostic value of repeated carotid intima-media thickness assessment in patients with coronary and extra coronary steno-occlusive arterial disease

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KEY WORDS

change in maximum carotid intima-media thickness, coronary artery diseases, major adverse cerebral and coronary events, peripheral artery disease, prospective evaluation

ABSTRACT

INTRODUCTION It is debatable whether the rate of change in carotid intima-media thickness (CIMT) may be used as a risk indicator of major adverse cerebral and coronary events (MACCEs) in patients with either coronary (CAD) and peripheral artery disease (PAD).

OBJECTIVES This prospective study aimed to evaluate the association between CIMT changes and the incidence of MACCEs, in patients with symptomatic CAD and PAD.

PATIENTS AND METHODS The study comprised 466 patients admitted with steno-occlusive disease, in whom revascularization was performed for an index lesion. Group 1 included 305 subjects with CAD, and group 2, 161 patients with PAD. CIMT was measured at baseline and at a median of 21 and 41 months afterwards. The incidence of MACCE, cardiovascular death (CVD), myocardial infarction (MI), and ischemic stroke was recorded prospectively during 5 years.

RESULTS CIMT increased with a mean (SD) progression rate of 0.027 (0.16) mm/y in group 1 and 0.026 (0.17) mm/y in group 2 ($P = 0.89$). CIMT regression was recorded in 112 patients (36.7%) and 61 patients (37.9%) in groups 1 and 2, respectively, at baseline ($P = 0.80$), and 82 patients (26.9%) and 42 patients (26.1%) in groups 1 and 2, respectively, in follow-up ($P = 0.85$). Maintained CIMT regression was independently associated with a reduced risk of MACCEs (hazard ratio [HR], 0.25; 95% CI, 0.15–0.42), MI (HR, 0.32; 95% CI, 0.20–0.51), ischemic stroke (HR, 0.29; 95% CI, 0.18–0.45), and CVD (HR, 0.24; 95% CI, 0.15–0.40), while the CIMT progression rate of 0.056 mm/y was associated with an increased risk of MACCEs (sensitivity, 53.2%; specificity, 72.2%; area under the receiver operating curve, 0.65).

CONCLUSIONS Maintained CIMT regression is associated with 68% to 75% reduction in the risk of a cardiovascular event. However, a long-term maintained CIMT regression is achieved in one-fourth of patients with either CAD or PAD.

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Received: November 14, 2018.
Revision accepted: December 17, 2018.
Published online: December 29, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2019; 129 (1): 12-21
doi:10.20452/pamw.4407

INTRODUCTION Atherosclerotic progression is the main factor responsible for ischemic cardiovascular events, such as major adverse cerebral and coronary events (MACCEs), as well as chronic ischemia.[1] There is evidence for a relationship between atherosclerotic development and peripheral artery stiffness, and endothelial dysfunction and intima-media thickness in carotid (CIMT) or femoral arteries.[2]

CIMT, reflecting vascular age, is independently associated with the extent of atherosclerosis and ischemic cardiovascular events.[3-9] According to current guidelines, in patients with symptomatic atherosclerotic lesions and risk factors,

rigorous control of risk factors with best medical treatment (BMT) and nonpharmacologic interventions are recommended.[10,11]

Many pharmacological agents have been shown to have beneficial effects on atherosclerotic plaques, slowing down their growth or even enabling plaque regression.[12-14] However, it is debatable whether growth slowing or plaque regression in CIMT might be related to the substantial reduction in the prevalence of MACCEs. Available data from previously published studies are unclear.[15-16] In patients receiving BMT with CIMT progression or regression, the risk of MACCEs is still unknown.

Therefore, the main objective of the present study was to evaluate whether change in CIMT assessed during serial measurements can be related to MACCE prevalence in patients with confirmed significant coronary artery disease (CAD) or extra coronary lesions exceeding 50% lumen reduction. Another goal of the present study was to assess what proportion of patients on BMT achieved regression in CIMT and whether this effect was durable.

PATIENTS AND METHODS This prospective study comprised 466 consecutive patients (277 men; mean [SD] age, 63.4 [9.6] years) admitted between the years 2010 and 2011, with suspected symptomatic steno-occlusive disease in at least 1 major arterial territory (including coronary, carotid, lower extremities, or renal), referred to our institution for further assessment and adequate treatment, including BMT and revascularization.

Group 1 comprised 305 patients: 207 men (mean [SD] age, 64.5 [9.5] years), with confirmed symptomatic significant CAD (at least 50% lumen reduction in a major coronary artery). Group 2 comprised 161 patients: 70 men (mean [SD] age, 61.3 [9.5] years), with no significant CAD but evidence of atherosclerotic lesions in the other major arterial territories among carotid, renal, or lower extremity arteries exceeding at least 50% lumen reduction.

The inclusion and exclusion criteria of the study, as well as study design, are presented in **FIGURE 1**.

The prevalence of cardiovascular risk factors was evaluated. Cardiovascular risk factors were defined as hypertension (treated or newly recognized, based on the average of 3 measurements; systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg), diabetes mellitus (treated or newly recognized; >11 mmol/l [200 mg/dl] in oral glucose tolerance test), hyperlipidemia (treated or newly recognized: total cholesterol >4.9 mmol/l [190 mg/dl] and/or low-density lipoprotein cholesterol (LDL) >3.0 mmol/l [115 mg/dl] and/or high-density lipoprotein cholesterol (HDL) men <1.0 mmol/l [40 mg/dl], HDL women <1.2 mmol/l [46 mg/dl], and/or triglycerides >1.7 mmol/l [150 mg/dl]).[17] Smoking was defined as current smoking or active smoking within the past 5 years.

Patients were prescribed long-term acetylsalicylic acid or clopidogrel and other medications, typically including a statin, β-blocker, sartans, and angiotensin-converting enzyme inhibitor (ACEI), as per current European Society Cardiology guidelines on the management of stable CAD or peripheral artery disease (PAD).[10,11]

All subjects gave their informed consent prior to enrollment in accordance with the requirements of the local ethics committee. The study was performed in line with the requirements of the Declaration of Helsinki.

Laboratory tests Blood samples were collected on admission to the Department, prior to any intervention, immediately after the signed informed consent was obtained from the patients. The following biochemical parameters were analyzed: serum creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, high-sensitivity C-reactive protein (hs-CRP), and triglycerides.

Carotid intima-media thickness assessment On admission, all patients underwent high-resolution B-mode, color Doppler, and pulsed-wave Doppler ultrasonography of the bilateral carotid arteries. The examination was performed using a Toshiba Aplio 300 ultrasound machine (Toshiba Medical Systems Co, Ltd, Ōtawara, Japan) equipped with a 4 to 12-MHz linear array transducer.

The maximum carotid intima-media complex (CIMT) of the near and far walls was measured in the distal 1 cm of the common carotid artery, at the bifurcation, and at the level of the internal carotid artery and was expressed as the mean maximum CIMT.

The CIMT evaluation was repeated in all patients twice. The first follow-up measurement was performed between month 12 and 24 (median, 21 months), and the final, between month 36 and 48 (median, 41 months).

The annual change in CIMT (mm/y) was calculated by using the following equation: annual change of CIMT = (follow-up CIMT – baseline CIMT)/follow-up period in years.

The difference between the follow-up and baseline CIMT was also expressed as an absolute Δ value according to the following equation: ΔCIMT = follow-up CIMT – baseline CIMT.

The ΔCIMT at follow-up was interpreted according to the following definition: growth slowing or regression was defined as ΔCIMT change equal to or less than 0.000 mm in every measurement. Progression was defined as an absolute CIMT increase above at least 0.001 mm in any measurement.

Assessment of atherosclerosis in major arterial territories At baseline, all patients were examined for concurrent steno-occlusive atherosclerotic disease in other major arteries. Diagnoses of CAD, renal, or supra-aortic (carotid or vertebral) artery stenosis, and PAD were based on a history of revascularization or the presence of

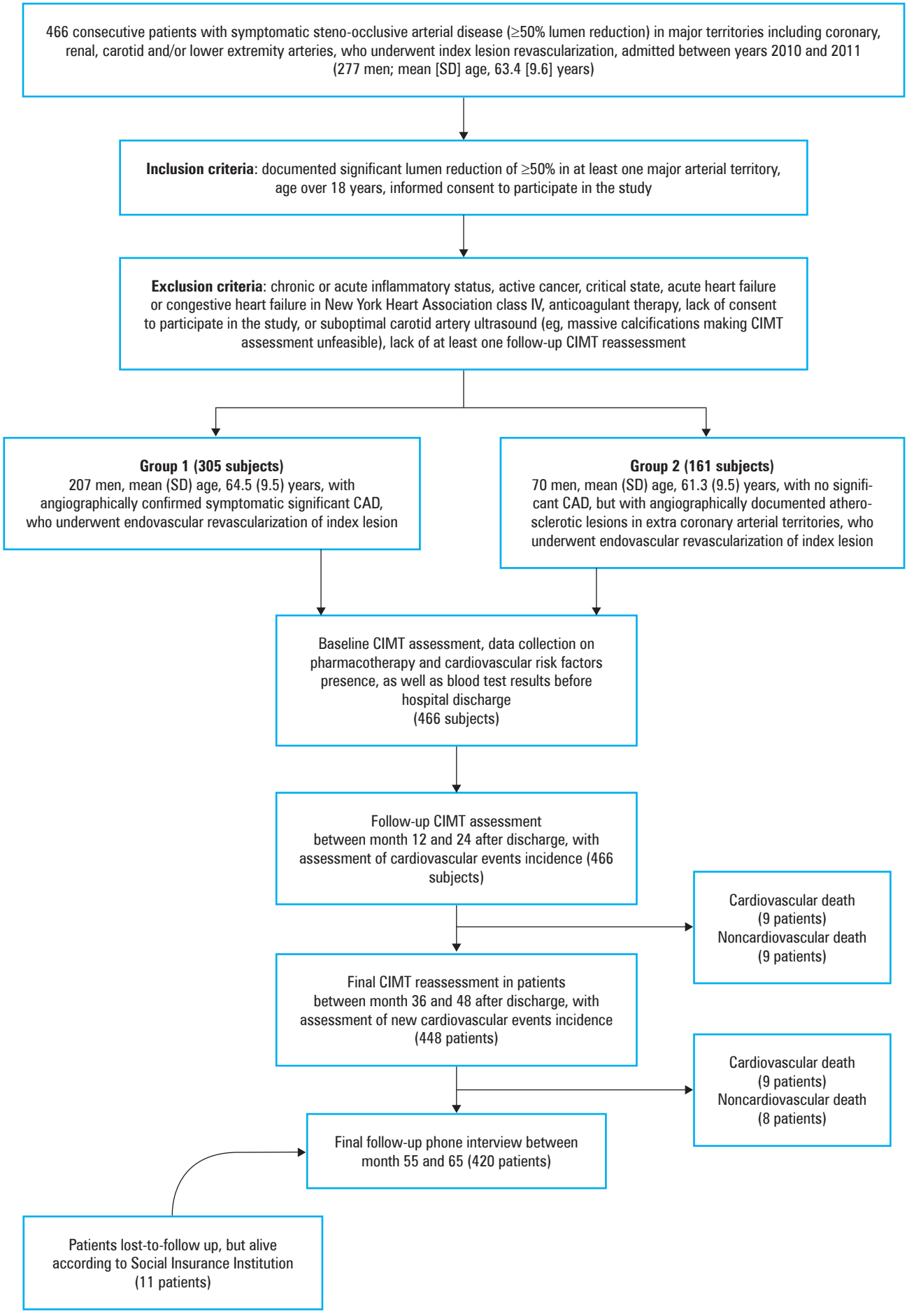

FIGURE 1 Study design, inclusion and exclusion criteria
Abbreviations: CIMT, carotid intima-media thickness; others, see **TABLE 1**

substantial atherosclerotic lesions. This was defined as at least 50% vascular lumen reduction in the corresponding territory as assessed by duplex ultrasonography, computed tomography angiography, or invasive angiography.

Additionally, the ankle–brachial index was routinely evaluated in all patients as a screening tool for PAD, with a cutoff value of less than 0.9. Verification of PAD diagnosis with Doppler ultrasound was performed in all cases with an ankle–brachial index of less than 0.9.

Stenoses of carotid, renal, and lower extremity arteries assessed as substantial by Doppler ultrasound based on the peak systolic and end-diastolic velocities were then verified by angiography or computed tomography angiography.

Coronary and peripheral angiography was performed from radial or femoral vascular access using a Coroscop system (Siemens AG, Munich, Germany) equipped with Quantcor version 4.0 quantitative analysis software. Angiography was performed in at least 2 orthogonal projections that best displayed the lesion.

Follow-up period During the mean (SD) follow-up of 57 (25) months (range, 13–84 months), the incidence of all MACCEs, including myocardial infarction (MI), ischemic stroke (IS), and cardiovascular death (CVD) were recorded.

MI was diagnosed according to the current criteria of the European Society of Cardiology.[18] The diagnosis of IS was established by a neurologist to ensure validity. CVD was defined as fatal IS, fatal MI, or other CVD (ie, any sudden or unexpected death unless proven as noncardiovascular on autopsy).

Data on MACCEs were collected during the ultrasound visits. As the study was continued beyond the last CIMT assessment, the final visit had a form of a telephone conversation with a patient or a family member. The survival status of patients lost to follow-up (n = 11) was determined on the basis of data obtained from the national health registry.

Patients were encouraged to adhere to the medications prescribed on discharge and intensify their efforts to achieve therapeutic goals. They were recommended to continue the Mediterranean diet and implement lifestyle changes throughout the follow-up.

Statistical analysis We analyzed the effect of CIMT change and patient-related factors on the incidence of the following endpoints: MACCEs, MI, IS, and CVD.

The *t* test was used for a comparison of continuous variables, and the χ^2 test was used to compare proportions of categorical variables. The means of the analyzed parameters across the groups were tested by the analysis of variance. Frequencies were compared by the χ^2 test for independence.

To establish the factors that could affect MACCEs, MI, IS, and CVD incidence, the clinical, procedural, and angiographic variables were assessed by a Cox univariate hazard analysis, and in cases with a trend towards a difference ($P < 0.05$), they were included in a multivariate stepwise Cox proportional hazards analysis. The results of the latter were expressed as hazard ratio (HR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curves were constructed to establish the best cutoff value for annual CIMT progression rate predicting risk of MACCEs. The area under the ROC curve (AUC) was calculated. Statistical analyses were performed with Statistica version 12.0 software (StatSoft, Inc, Tulsa, Oklahoma, United States). A *P* value of less than 0.05 was considered significant.

RESULTS Subjects in group 1, as compared to group 2 were significantly older ($P < 0.001$), showed a significant increase in prevalence of classic cardiovascular risk factors such as: hypertension ($P = 0.02$), diabetes ($P = 0.002$), hyperlipidemia ($P < 0.001$), smoking ($P = 0.01$), and had a higher number of arterial territories with substantial stenosis ($P < 0.001$) (TABLE 1). The detailed clinical characteristics and assessment of concurrent substantial atherosclerosis of the study group are summarized in TABLE 1. On discharge, long-term acetylsalicylic acid and/or clopidogrel was given in all subjects; ACEI, in 74.6%; sartans, in 5.4%; β-blocker, in 72.4%; statins, in 94.6%; fibrates, 2.5%; ezetimibe, 3.2%; diuretics, 46.9%; and calcium channel blockers, in 46.9% of the patients.

The baseline mean (SD) CIMT value in group 1 was higher than in group 2: 1.475 (0.42) vs 1.318 (0.44), $P < 0.001$, as well as mean CIMT values after the first and second re-evaluation follow-up CIMT (FIGURE 2).

During the first follow-up visit, the mean CIMT value regression was found in 112 patients (36.7%) in group 1 and in 61 patients (37.9%) in group 2 ($P = 0.80$), while in the remaining patients, CIMT progression was observed despite BMT (FIGURE 3).

On final CIMT reassessment, CIMT regression was maintained in 82 patients (26.9%) in group 1 and in 42 patients (26.1%) in group 2, while CIMT progression was observed in 223 patients (73.1%) and 119 patients (73.9%), respectively ($P = 0.85$) (FIGURE 3).

Overall, the mean CIMT value was progressing, with a mean (SD) progression rate similar in both groups: +0.027 (0.16) mm/y vs +0.026 (0.16) mm/y; $P = 0.89$. CIMT progression was related to significantly higher incidence of MACCEs, MI, and IS in both groups, as compared with patients with CIMT regression (FIGURE 4).

CIMT progression was an independent risk factor of future MACCEs in multivariate stepwise regression analysis (RR, 1.22; 95% CI, 1.03–1.44; $P < 0.001$). In the ROC analysis, the annual mean CIMT progression rate of 0.056 mm/y was the best predictor of MACCEs; however, this had moderate sensitivity (53.2%) and specificity (72.2%) (AUC, 0.646). Data are shown in FIGURE 5.

TABLE 1 Baseline characteristics of the study group (n = 466)

Parameter	All patients (n = 466)	Group 1 CAD (+) (n = 305)	Group 2 PAD (+) (n = 161)	*P* value
Demographic data				
Age, y, mean (SD); range	63.4 (9.6); 0–89	64.5 (9.5); 37–89	61.3 (9.5); 0–87	<0.001
Male sex, n (%)	277 (59)	207 (68)	70 (43)	<0.001
Clinical data, n (%)				
Hypertension	436 (94)	291 (95)	145 (90)	0.02
Diabetes mellitus	140 (30)	106 (35)	34 (21)	<0.01
Hyperlipidemia	415 (89)	285 (93)	130 (81)	<0.001
Smoking (current or in the past 5 years)	257 (55)	181 (59)	76 (47)	0.01
Body mass index, kg/m^2, mean (SD)	27.5 (3.9)	27.6 (3.9)	27.4 (3.8)	0.72
Previous MI	155 (33.3)	155 (51)	0	<0.001
Previous IS	106 (23)	67 (22)	39 (24)	0.58
Number of coronary arteries with >50% stenosis, n (%)				
1-vessel CAD	107 (22)	107 (35.1)	NA	NA
2-vessel CAD	63 (14)	63 (21)		
3-vessel CAD	135 (29)	135 (45)		
Number of arterial territories with lumen reduction >50%				
1 territory, n (%)	165 (32)	61 (20)	116 (72)	<0.001
2 territories, n (%)	156 (33)	135 (44)	32 (20)	
3 territories, n (%)	91 (19)	83 (27)	13 (8)	
4 territories, n (%)	25 (5)	26 (9)	0	
Ankle–brachial index, mean (SD)	0.96 (0.21)	1.05 (0.20)	0.84 (0.21)	<0.001
LVEF, %, mean (SD)	58 (10)	56 (10)	63 (9)	<0.001
Laboratory data, mean (SD)				
hs-CRP, mg/l	4.62 (8.43)	5.06 (9.7)	3.8 (5.2)	0.09
Creatinine, µmol/l	93.3 (33.2)	96.8(33.1)	86.5 (32)	0.004
TC, mmol/l	4.84 (1.18)	4.87 (1.2)	4.77 (1.05)	0.47
LDL-C, mmol/l	2.91 (0.97)	2.94 (1.0)	2.84 (0.94)	0.31
HDL-C, mmol/l	1.25 (0.35)	1.22 (0.3)	1.32 (0.35)	0.31
Triglycerides, mmol/l	1.59 (1.05)	1.64 (1.2)	1.48 (0.73)	0.05
Medications prescribed on discharge, n (%)				
Acetylsalicylic acid / clopidogrel	466 (100)	305 (100)	161 (100)	1.00
ACEI	348 (74.6)	265 (86.9)	79 (49.1)	<0.001
Sartan	25 (5.4)	12 (3.9)	13 (8.1)	0.06
β-blocker	338 (72.5)	254 (83.3)	84 (52.2)	<0.001
Statin	441 (94.6)	295 (96.7)	146 (90.7)	0.006
Fibrate	12 (2.5)	8 (2.6)	4 (2.5)	0.92
Ezetimibe	15 (3.2)	3 (0.9)	12 (7.4))	<0.001
Diuretic	219 (46.9)	151 (49.5)	68 (42.2)	0.13
Calcium channel blocker	218 (46.8)	132 (43.3)	86 (53.4)	0.037

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; PAD, peripheral artery disease; TC, total cholesterol

The Cox univariate regression analysis indicated that maintained mean CIMT regression during follow-up visits is a potentially better prognostic factor of MACCEs, CVD, IS, and MI associated with risk reduction (TABLE 2). Also, history of hyperlipidemia (P = 0.005), cigarette usage (P = 0.0005), and male sex (P = 0.046) were associated with MACCEs. The association of MI risk with smoking tended to be significant (P = 0.08).

In a multivariate stepwise Cox proportional hazards analysis, the maintained CIMT regression on two consecutive follow-up visits was independently associated with a reduced risk of MACCEs (HR, 0.25; 95% CI, 0.15–0.42; P <0.001), MI (HR, 0.32; 95% CI, 0.20–0.51; P <0.001), IS (HR, 0.29; 95% CI, 0.18–0.45; P <0.001), and CVD (HR, 0.24; 95% CI, 0.15–0.40; P<0.001). Other independent predictors of MACCEs, CVD, MI, and IS are given in FIGURE 6.

DISCUSSION The major finding of the present study, conducted on revascularized patients on BMT with significant CAD or PAD, is that maintenance of CIMT regression on consecutive ultrasonographic examinations during the median 21- and 41-month follow-up, is associated with a significant reduction in risk of MACCEs, MI, IS, and CVD, as compared to CIMT progression. Unfortunately, the maintained CIMT regression was noted in approximately one-fourth of our study participants.

The number of patients who achieve CIMT reduction varies in reported studies. In a study by Bovesky et al, regression of common CIMT was noted in only 7.8% of patients with type 2 diabetes.[19] The MITEC trial[20] showed a reduction in CIMT in 56.5% of patients on candesartan and 59% on amlodipine. Also, Schneider et al[21] showed a significant, BMT-induced reduction of the common CIMT in a group of 298 patients with non–ST-segment elevation MI at 12 months in comparison with the baseline values.[21]

However, in the aforementioned studies, CIMT assessment was performed only once during the follow-up.

Our study also indicated that only maintenance of CIMT regression is a really valuable marker of lower cardiovascular event risk. Maintained CIMT regression, in comparison with CIMT progression, was associated with a 68% to 76% reduction in cardiovascular risk in a multivariate Cox proportional hazards analysis during the 5-year follow-up.

In the Cholesterol Lowering Atherosclerosis Study (CLAS) trial,[20] featuring therapy with colestipol-niacin, a lower rate of change in common CIMT over time was related to a lower risk of an event during the 8.8-year follow-up.[20] Patients with an annual common CIMT progression rate of 0.034 mm/y had a 2.9-fold higher CVD risk compared with those with a common CIMT progression rate of 0.011 mm/y or less.[22]

However, the present study indicated that nearly three-fourth of patients had CIMT progression despite receiving treatment. This proportion remained similar in both study groups and was related to a significantly higher prevalence of

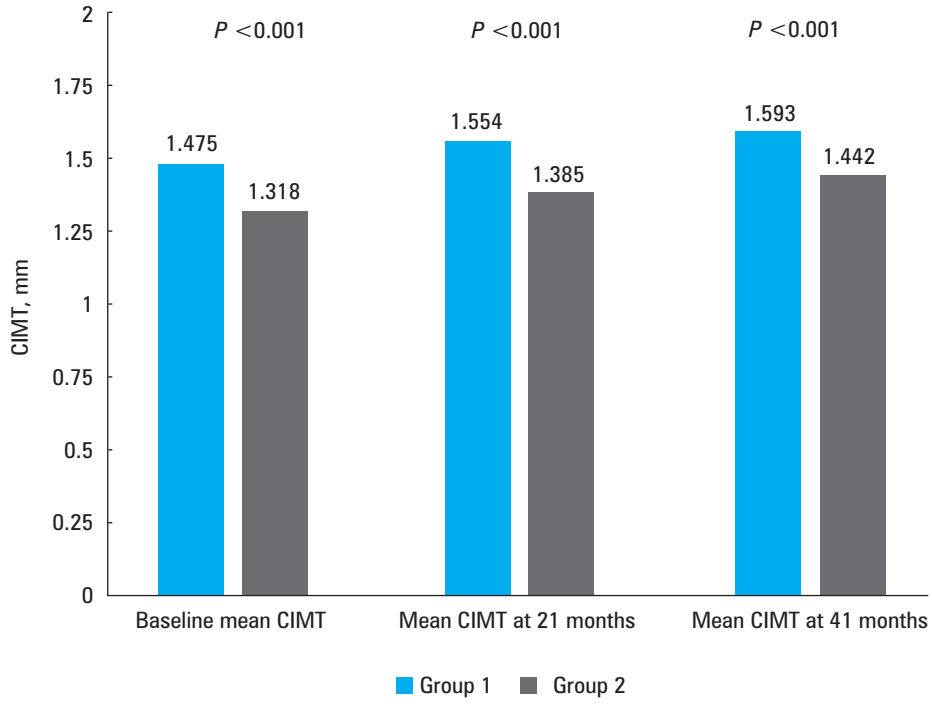

FIGURE 2 Initial mean carotid intima-media thickness (CIMT) value and CIMT changes during follow-up visits

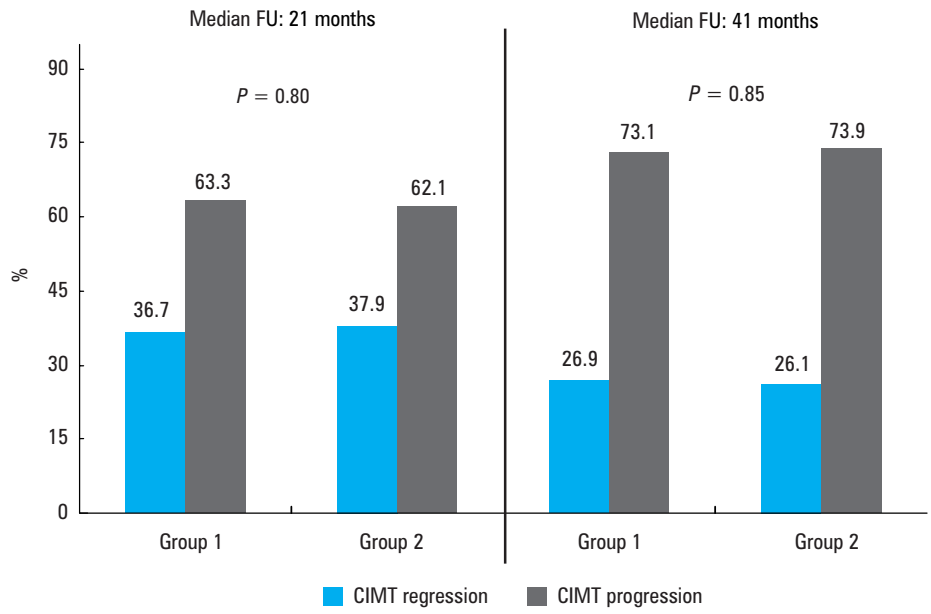

FIGURE 3 Proportion of patients in group 1 and group 2 in whom carotid intima-media thickness (CIMT) regression vs progression was observed at a median follow-up (FU) of 21 months and 41 months

MACCEs. Although the annual mean CIMT progression rate of 0.056 mm/y was the best predictor of MACCEs, it was characterized by a relatively low sensitivity (53.2%) and specificity (72.2%).

Consistent with our results, Okayama et al[23] observed that a higher median progression rate of common CIMT (0.03 mm/y) was a significant determinant of MACCEs (HR, 2.24; 95% CI, 1.25–4.03; P <0.01) during a mean follow-up of 7.6 years (in a multivariate Cox proportional hazard model). Additionally, the combination of high baseline CIMT (above 1.1 mm) and high CIMT progression (>0.034 mm/y) was a significant predictor of MACCEs.[23]

A higher clinical value of CIMT was found in a study by Hirano et al,[24] including 240 patients with CAD who had a carotid plaque (CIMT ≥1.1 mm) at baseline.[24] Researchers found that fast max-aggregate CIMT progression after 6 months (2nd CIMT test) was a significant predictor of coronary events during a 2-year follow-up after adjustment for known risk factors (HR per 0.1-mm increase over 6 months, 1.21; 95% CI, 1.10–1.33; P = 0.0001).[25] In that study, ROC curves showed that the addition of the change in plaque-CIMT max to conventional risk factors resulted in a greater AUC compared with conventional Framingham risk factors alone (0.81 and 0.70, respectively, P = 0.02).[24]

Interestingly, in the IMPROVE study,[25] the assessment of the 15-month progression demonstrated that only the fastest CIMT maximum progression was significantly associated with the risk of subsequent vascular events.[25] Yet, Bartman et

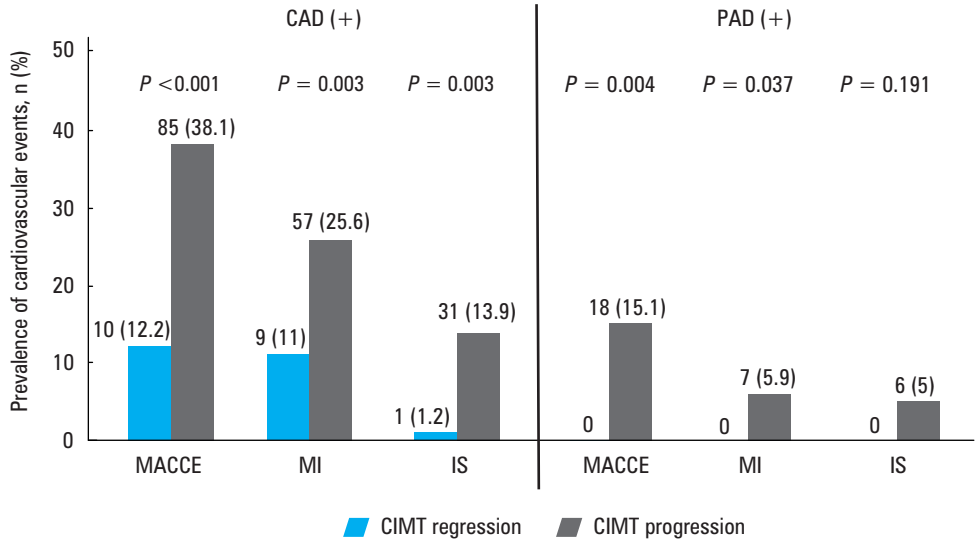

FIGURE 4 Number of patients with major adverse cerebral and coronary events, myocardial infarction, and ischemic stroke depending on the observed change in final follow-up carotid intima-media thickness (CIMT) assessment with respect to significant coronary artery disease presence on initial coronary angiography
Abbreviations: MACCE, major adverse cerebral and coronary events; others, see **TABLE 1**

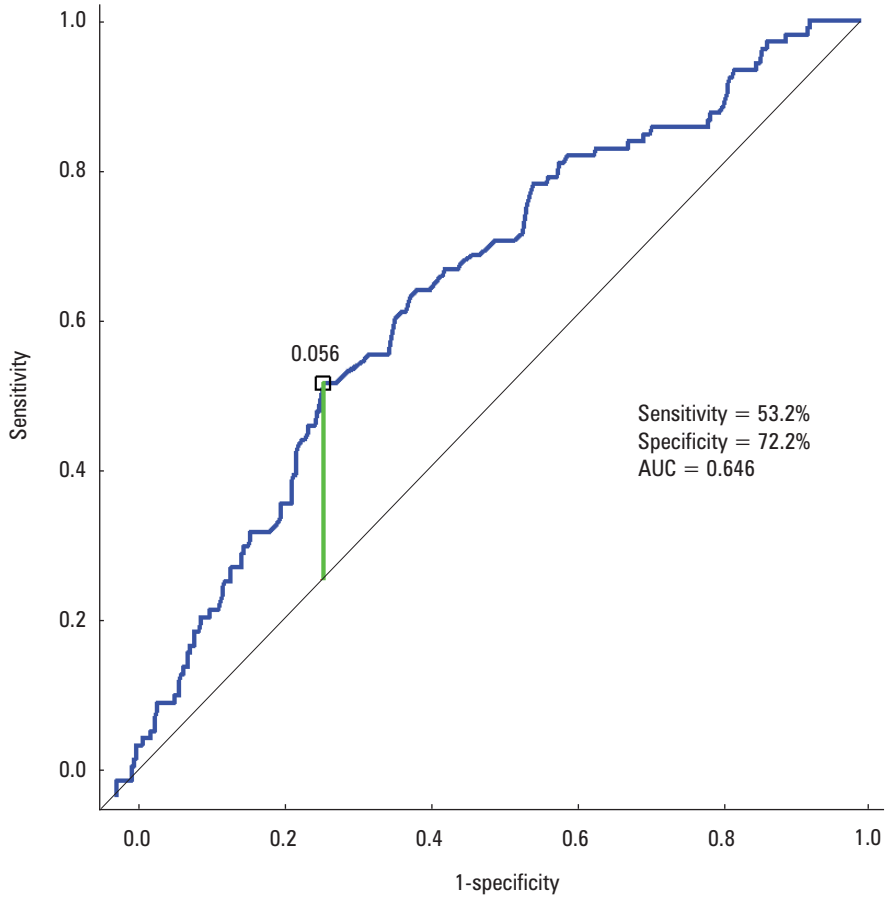

FIGURE 5 A receiver operating characteristic curve (ROC) for annual carotid intima-media thickness (CIMT) progression and major adverse cerebral and coronary events
Abbreviations: AUC, area under the receiver operating characteristic curve

al[26] reported that, unlike CIMT, the carotid plaque score was independently associated with micro-angiopathic complications in type 2 diabetes.[26]

A different approach to CIMT assessment was presented by Wannarong et al.[27] They observed that progression of total carotid plaque area at 1-year follow-up was a significant predictor of vascular events after adjustment for coronary risk factors (P = 0.001), but the progression or regression of the CIMT itself did not predict IS, transient ischemic attack, death, or any cardiovascular events.[27] Also, in the present study, the inclusion of carotid plaque into CIMT measurement was shown to be an important prognostic marker. This is in line with a recent meta-analysis showing that carotid plaque, compared with CIMT, more accurately predicts coronary artery disease events.[28]

The potential advantage of CIMT changes monitoring is the reassessment of risk in an individual patient. Of note, CIMT progression or regression is a complex process, as it depends on multiple

TABLE 2 Associations between clinical, laboratory, and carotid intima-media thickness parameters and major adverse cerebral and coronary events, myocardial infarction, ischemic stroke, and cardiovascular death in univariate Cox proportional hazards analysis

Parameter	MACCE	CVD	MI	IS
Mean CIMT regression on the first follow-up visit	0.249 (0.15–0.39); <0.001	0.42 (0.28–0.63); <0.001	0.37 (0.24–0.58); <0.001	0.29 (0.19–0.46); <0.001
Maintained mean CIMT regression on the final visit	0.311 (0.19–0.49); <0.001	0.46 (0.31–0.67); <0.001	0.41 (0.27–0.63); <0.001	0.36 (0.24–0.54); <0.001
Age	1.02 (1.01–1.02); <0.001	1.02 (1.01–1.04); <0.001	1.02 (1.01–1.08); <0.001	1.02 (1.01–1.04); <0.001
Female sex	0.80 (0.65–0.98); <0.001	0.86 (0.71–1.04); 0.13	0.79 (0.65–0.97); 0.02	0.89 (0.73–1.08); 0.26
Hypertension	0.96 (0.63–1.45); 0.84	0.93 (0.64–1.35); 0.71	1.01 (0.69–1.49); 0.92	0.84 (0.58–1.28); 0.47
Diabetes mellitus	1.00 (0.79–1.26); 0.96	0.97 (0.79–1.19); 0.77	0.95 (0.77–1.73); 0.67	0.99 (0.80–1.22); 0.96
Hyperlipidemia	1.37 (1.01–1.89); 0.048	1.21 (0.90–1.63); 0.20	1.27 (0.99–1.730; 0.13	1.31 (0.97–1.76); 0.08
Smoking	1.21 (0.98–1.49); 0.06	1.11 (0.93–1.34); 0.25	1.16 (0.95–1.42); 0.13	1.13 (0.93–1.37); 0.049
Creatinine	1.00 (0.99–1.00); 0.19	1.00 (0.99–1.00); 0.13	1.00 (0.99–1.00); 0.29	1.00 (0.99–1.01); 0.08
hs-CRP	0.99 (0.98–1.01); 0.04	0.99 (0.98–1.01); 0.54	0.99 (0.98–1.01); 0.79	0.99 (0.98–1.01); 0.51
TC	1.00 (0.99–1.00); 0.59	1.00 (0.99–1.00); 0.69	1.00 (0.99–1.00); 0.21	1.00 (0.99–1.00); 0.68
LDL-C	1.00 (0.99–1.00); 0.18	1.00 (0.99–1.00); 0.26	1.00 (0.99–1.00); 0.21	1.00 (0.99–1.00); 0.24
HDL-C	1.00 (0.99–1.00); 0.18	1.00 (0.99–1.00); 0.24	1.00 (0.99–1.00); 0.21	1.00 (0.99–1.00); 0.23
Glucose	1.02 (0.94–1.11); 0.57	1.02 (0.95–1.09); 0.57	1.02 (0.95–1.11); 0.48	1.01 (0.93–1.09); 0.78
Statin use	0.53 (0.20–1.48); 0.23	0.01 (0.00–996); 0.99	0.64 (0.21–2.03); 0.45	0.32 (0.04–2.31); 0.26

Data are presented as HR (95% CI); *P* value.

Abbreviations: CVD, cardiovascular death; others, see TABLE 1, FIGURES 1 and 3

factors.[29,30] The final effect on CIMT depends on the action of proatherosclerotic demographic, cardiovascular, and genetic risk factors as well as the achievement of the therapeutic goals through the use of medications and lifestyle changes. From this perspective, CIMT changes only demonstrate whether our pharmacological and nonpharmacological interventions are sufficient to limit atherosclerosis progression or not. CIMT does not support any data on which the mechanism of atherosclerosis progression is a key factor in an individual patient. Probably, for these reasons, in the current study, statins failed to show an independent effect on MACCE incidence. The same finding was reported by Hirano et al,[24] who demonstrated that CIMT changes, despite antiatherosclerotic therapy, are independently associated with future coronary events. Moreover, the use of statin and ACEI or sartans had no significant incremental effect on predicting future coronary events.[24]

Thus, the possible role of a change in the CIMT is to warrant a closer "look" at patient compliance and improve medications to achieve therapeutic goals.

In conclusion, we showed that repeated assessment of CIMT changes during follow-up both in patients with CAD and substantial PAD might be a valuable tool for cardiovascular event risk assessment in individual subjects. We demonstrated that a durable CIMT regression effect is achieved in only one-fourth of subjects. However, maintained CIMT regression is a more valuable clinical marker of treatment efficacy, related to lower cardiovascular event risk, as compared to CIMT progression which is only moderately associated with increased risk of MACCEs.

Study limitations The length of CIMT measurement intervals was not predefined. Only baseline risk factor levels and medications were used for all analyses. The aim of the study was not to investigate links between achieved therapeutic goals, CIMT changes and their effect on MACCE.

ACKNOWLEDGMENTS Research grant from the Jagiellonian University (grant no. K/ZDS/005730; to AK-Z). The results were previously presented at conferences: European Society of Cardiology in Munich

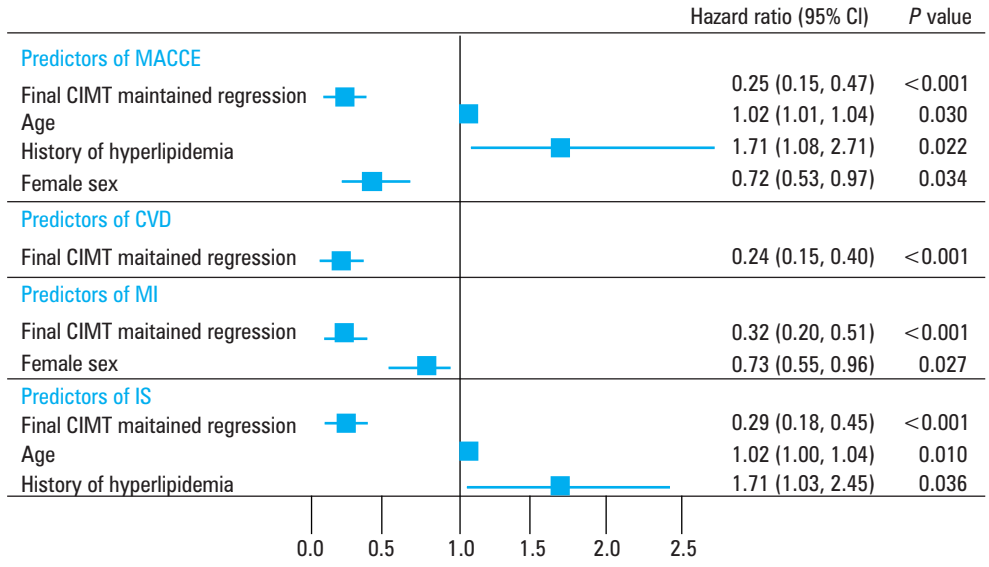

FIGURE 6 Independent associations between clinical, laboratory, and carotid intima–media thickness parameters and major adverse cerebral and coronary events, myocardial infarction, ischemic stroke, and cardiovascular death in multivariate Cox proportional hazards analysis. Abbreviations: see **TABLE 1**, **TABLE 2**, **FIGURE 1**, and **FIGURE 4**

2018 (doi.org/10.1093/eurheartj/ehy566.6154) and the International Congress of the Polish Cardiac Society in Kraków 2018.

CONTRIBUTION STATEMENT JG contributed to study concept and design, performance of examinations, CIMT measurements, data collection, obtaining the informed consent, obtaining blood samples and preparing biological material for further laboratory analyses, and manuscript writing. TP contributed to study concept and design, work supervision, interpretation of data for the final approval of the version to be published, responsibility for data integrity supervision. JP and RB performed examinations, collected data for statistical analyses, and drafted the article. PP contributed to analysis and editing assistance, as well as critical revision for important intellectual content. SM contributed to data collection for statistical analyses and manuscript drafting. WR contributed to critical revision for important intellectual content, and statistical analysis. KŻ contributed to the assessment of coronary angiographies, writing and editing assistance, and critical revision of the work. AK-Z contributed to study concept and design, obtaining funds, analysis and interpretation of the data, CIMT measurements and data reproducibility, manuscript writing, and was responsible for all aspects of the work, its integrity and accuracy, and appropriateness of investigations and resolves, as well as the final manuscript approval.

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