

Intima-media thickness and ankle-brachial index are correlated with the extent of coronary artery disease measured by the SYNTAX score

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Abstract

Introduction: The extent of peripheral artery disease (PAD) measured by the ankle-brachial index (ABI) and intima-media thickness (IMT) is correlated with the complexity of coronary artery disease (CAD) in stable angina patients. However, data regarding patients with acute coronary syndromes are still lacking.

Aim: To compare coronary complexity measured by the SYNTAX score in patients with and without PAD presenting with myocardial infarction (MI).

Material and methods: Both ABI and IMT were measured in 101 consecutive patients who underwent primary diagnostic due to MI. Patients were divided into three tertile groups depending on the SYNTAX score (0–4; 5–11; 12 and more points).

Results: Mean ABI in the general population was 0.9 ± 0.26 , mean IMT was 0.8 ± 0.3 mm and mean SYNTAX score was 7.8 ± 5.4 points. We found significant correlations between ABI and SYNTAX score ($p = 0.01$), IMT and SYNTAX score ($p < 0.001$), and IMT and ABI ($p < 0.001$). The highest mean values of IMT ($p < 0.001$) and lowest mean values of ABI ($p = 0.015$) were found in patients in the highest SYNTAX score group. When analyzing receiver operating characteristics (ROC) curves, IMT had greater specificity and sensitivity than ABI.

Conclusions: Both IMT and ABI are correlated with SYNTAX score (positively for IMT and negatively for ABI values). In our study, IMT was a better predictor of SYNTAX score than ABI. Our study suggests that the higher rate of cardiovascular events in patients with PAD presenting with MI may be partially explained by greater coronary lesion complexity.

Key words: coronary artery disease, acute coronary syndrome, carotid intima-media thickness, peripheral artery disease, ankle-brachial index, SYNTAX score.

Introduction

Peripheral artery disease (PAD) measured by the ankle-brachial index (ABI) is an important marker of cardiovascular mortality and morbidity and is positively associated with the extent of coronary artery disease (CAD) [1, 2]. Most of the events in PAD patients are attributed to coronary atherosclerosis – which means that the cardiovascular risk profile is more pronounced in concomitant CAD and PAD [3–7]. The complexity of CAD may be measured by the Synergy Between PCI With

TAXUS and Cardiac Surgery (SYNTAX) score, which is used as a prognostic tool in the short- and long-term risk stratification in patients who underwent coronary intervention [8]. Interestingly, this scoring system has been positively associated with PAD [9, 10]. There is substantial evidence that carotid intima-media thickness (IMT) is, similarly to ABI, associated with SYNTAX score and may be considered as a marker of increased cardiovascular risk [11, 12]. Moreover, IMT is a recommended measure of vascular age, which is usually different from the metric one, and thus may allow one to

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identify individuals with advanced subclinical atherosclerosis and as such to alternate cardiovascular risk estimates [13]. Measuring IMT and ABI may be an easy method to predict the extent of CAD and possible future cardiac events in patients with stable angina [14]. However, data regarding patients with acute coronary syndromes are still lacking.

Aim

Therefore, we sought to assess whether measuring both IMT and ABI may predict the extent of CAD in patients undergoing primary percutaneous coronary intervention (PCI) due to myocardial infarction (MI).

Material and methods

All data were gathered in a single cardiology center. Both ABI and IMT were measured in 101 consecutive patients who underwent primary PCI due to MI – with ST-segment elevation (STEMI) or without ST-segment elevation (NSTEMI). Patients who died during hospitalization, were hemodynamically unstable, or could not have ABI or IMT measured were excluded. All patients provided written informed consent to participate. The study followed the ethical principles for clinical research based on the Declaration of Helsinki. No funding was used to support this research.

During the hospital stay (more than 3 days after the procedure), after 10 min rest in a horizontal position ABI was measured on the posterior and anterior tibial artery of both legs and the brachial artery of both arms using a volume plethysmograph. ABI was measured twice by two different physicians. The second measurement was taken 5 min after the first one. For the study, the lowest ABI obtained for either side was reported.

To avoid bias in measurements, IMT was assessed by two sonographers who had no knowledge of the results of either the ABI measurements or the IMT measurements of the other physician. Only one certified scanner (VIVID 7 DIMENSION, GE Healthcare, USA) was used. It was equipped with a 7.5-MHz linear array transducer. Patients were examined in the supine position with their heads tilted backward and rotated slightly to expose an area from the clavicle to the angle of the jaw. Firstly, the sonographer localized the carotid artery (CA) and its bifurcation using a transverse scan. After that, the probe was rotated 90° to obtain longitudinal images of the walls of the CA. The IMT was measured 1 cm under the bifurcation. The higher IMT (from the right or left common CA) was taken for the study.

The SYNTAX score was measured by two physicians who were blinded to the results of both IMT and ABI measurements. The score was calculated using the algorithm available on the SYNTAX website [15]. The angiographic films just before stent implantation were used to score the culprit lesion [13].

Patients were stratified into two groups based on ABI ($>$ or \leq 0.9). In addition, patients were divided into three tertile groups depending on the SYNTAX score – low (0–4 points), medium (5–11 points) and high score (\geq 12 points).

To combine both IMT and ABI we used 4 groups as proposed by Ikeda *et al.* [16] – group A with IMT $<$ 0.9 mm and ABI \geq 0.9, group B with IMT $<$ 0.9 mm and ABI $<$ 0.9, group C with IMT \geq 0.9 mm and ABI \geq 0.9, group D with IMT \geq 0.9 mm and ABI $<$ 0.9.

Statistical analysis

All continuous variables are presented as mean with standard deviation (SD). Categorical variables are presented as percentages or number of patients. All variables were tested for normal distribution. For categorical variable comparison we used Fisher or χ^2 tests. The Kruskal-Wallis (nonparametric test) test was used to compare multiple groups. To compare continuous variables we used the 2-sample unpaired Student's *t*-test (normal distribution) or Mann-Whitney *U*-test. Correlations were tested using the Spearman rank order test. Two-sided $p < 0.05$ was considered significant. Receiver operating characteristics (ROC) curve analysis was used to assess the ability of ABI and IMT to predict SYNTAX score \geq 12 points. Area under the curve (AUC) and confidence intervals (CI) were calculated. The StatSoft Statistica package (version 10, StatSoft Inc., Tulsa, OK, USA) and IBM SPSS version 23 (IBM Corp. in Armonk, NY) were used.

Results

We recruited 101 patients, of whom 56 (55.4%) were males. Mean age was 64.7 ± 11.6 years, 53 (52.5%) out of 101 patients had hyperlipidemia, 28 (27.7%) had diabetes, and 24 (23.8%) were smokers. Out of the general population, in 34 (33.7%) patients the left anterior descending artery (LAD) was responsible for MI. The right coronary artery (RCA) was responsible for MI in 36 (35.6%) patients. There were 20 (19.8%) patients with the left circumflex artery (Cx) as the infarct-related artery (IRA). In 1 (1.0%) patient the left main (LM) coronary artery was identified as the infarct-related artery (IRA). Stents were deployed in 87 (86.1%) patients. Mean ABI in the general population was 0.9 ± 0.26 , mean IMT was 0.8 ± 0.3 mm and mean SYNTAX score was 7.8 ± 5.4 points. After dividing patients into two ABI and two IMT groups, patients' characteristics were comparable (Tables I and II). Interestingly, those patients with lower ABI or higher IMT had significantly higher troponin levels on admission. We observed a significant correlation between IMT and SYNTAX score, ABI and SYNTAX score, and ABI and IMT (Figure 1, Tables I and II). When combining both IMT and ABI, the highest mean SYNTAX score was in group D (11.9 ± 5.4 points). The mean score was 6.4 ± 4.0 for group A; 7.6 ± 3.8 for group B; and 11.7 ± 4.5 for group C ($p < 0.002$).

Table I. Baseline patients' characteristics according to ankle-brachial index

Parameter	ABI ≤ 0.9 (n = 45)	ABI > 0.9 (n = 56)	P-value
Age [years]	63.8 ±10.9	65.5 ±12.2	0.426
BMI [kg/m ²]	29.3 ±2.8	29.0 ±4.3	0.607
Gender (male), n (%)	29 (64.4)	70 (48.2)	0.056
Smokers, n (%)	13 (28.9)	11 (19.6)	0.242
Hyperlipidaemia, n (%)	23 (51.1)	30 (53.6)	0.983
Diabetes, n (%)	14 (31.1)	14 (25.0)	0.302
Arterial hypertension, n (%)	31 (68.9)	43 (76.8)	0.879
Previous PCI, n (%)	13 (28.9)	13 (23.2)	0.507
Previous MI, n (%)	16 (35.6)	19 (33.9)	0.626
Troponin cTnT on admission [µg/l]	2.7 ±5.1	0.99 ±1.9	0.003
IMT [mm]	0.93 ±0.25	0.69 ±0.24	< 0.001

Values are mean ± standard deviation (SD) or n (%). ABI – ankle-brachial index, BMI – body mass index, IMT – intima-media thickness, MI – myocardial infarction, PCI – percutaneous coronary intervention.

Table II. Baseline patients' characteristics according to intima-media thickness

Parameter	IMT ≤ 0.9 mm (n = 30)	IMT > 0.9 mm (n = 71)	P-value
Age [years]	68.4 ±10.8	63.3 ±11.6	0.056
BMI [kg/m ²]	29.2 ±3.4	29.1 ±4.0	0.862
Gender (male), n (%)	16 (53.3)	40 (56.3)	0.942
Smoker, n (%)	9 (30.0)	15 (21.1)	0.265
Hyperlipidaemia, n (%)	18 (60.0)	35 (49.3)	0.337
Diabetes, n (%)	11 (36.7)	17 (23.9)	0.084
Arterial hypertension, n (%)	25 (83.3)	49 (69.0)	0.103
Previous PCI, n (%)	9 (30.0)	17 (23.9)	0.577
Previous MI, n (%)	12 (40.0)	23 (32.4)	0.592
Troponin cTnT on admission [µg/l]	2.1 ±2.4	1.7 ±4.3	0.024
ABI	0.79 ±0.28	0.95 ±0.24	0.005

Values are mean ± standard deviation (SD) or n (%). ABI – ankle-brachial index, BMI – body mass index, IMT – intima-media thickness, MI – myocardial infarction, PCI – percutaneous coronary intervention.

Patients with ABI ≥ 0.9 had a lower SYNTAX score and IMT than patients with ABI < 0.9 (7.5 ±4.6 vs. 10.0 ±5.2 points; $p < 0.001$ and 0.7 ±2.5 mm vs. 0.9 ±2.4 mm; $p < 0.001$, respectively). Results showing low, intermediate and high SYNTAX scores combined with IMT and ABI are shown in Figure 2. Differences between groups were statistically significant with $p < 0.001$ for IMT and $p = 0.006$ for ABI. ROC curves for ABI, IMT and high SYNTAX score (12 points and more) were calculated (Figure 3). For prediction of a high SYNTAX score we achieved 60% sensitivity and 75% specificity with ABI < 0.7 (AUC = 0.637, 95% CI: 0.507–0.768; $p = 0.040$) and 86% sensitivity and 62% specificity with IMT > 0.75 mm (AUC = 0.796, 95% CI: 0.710–0.883; $p < 0.001$).

Discussion

Patients with PAD are known to have a greater plaque burden and inflammatory burden, and worse endothelial function, which may explain the higher frequency cardiovascular events in those patients [17, 18]. SYNTAX score has consistently been shown to be an independent predictor of adverse events such as MI and target-lesion revascularization (TLR), both in short-term and long-term follow-up [19–21]. This score is assessed based on the anatomy of coronary arteries and lesion types; thus predicting the SYNTAX score might be helpful before preparing for elective procedures. Several studies have reported a correlation between IMT or ABI and SYNTAX score [16,

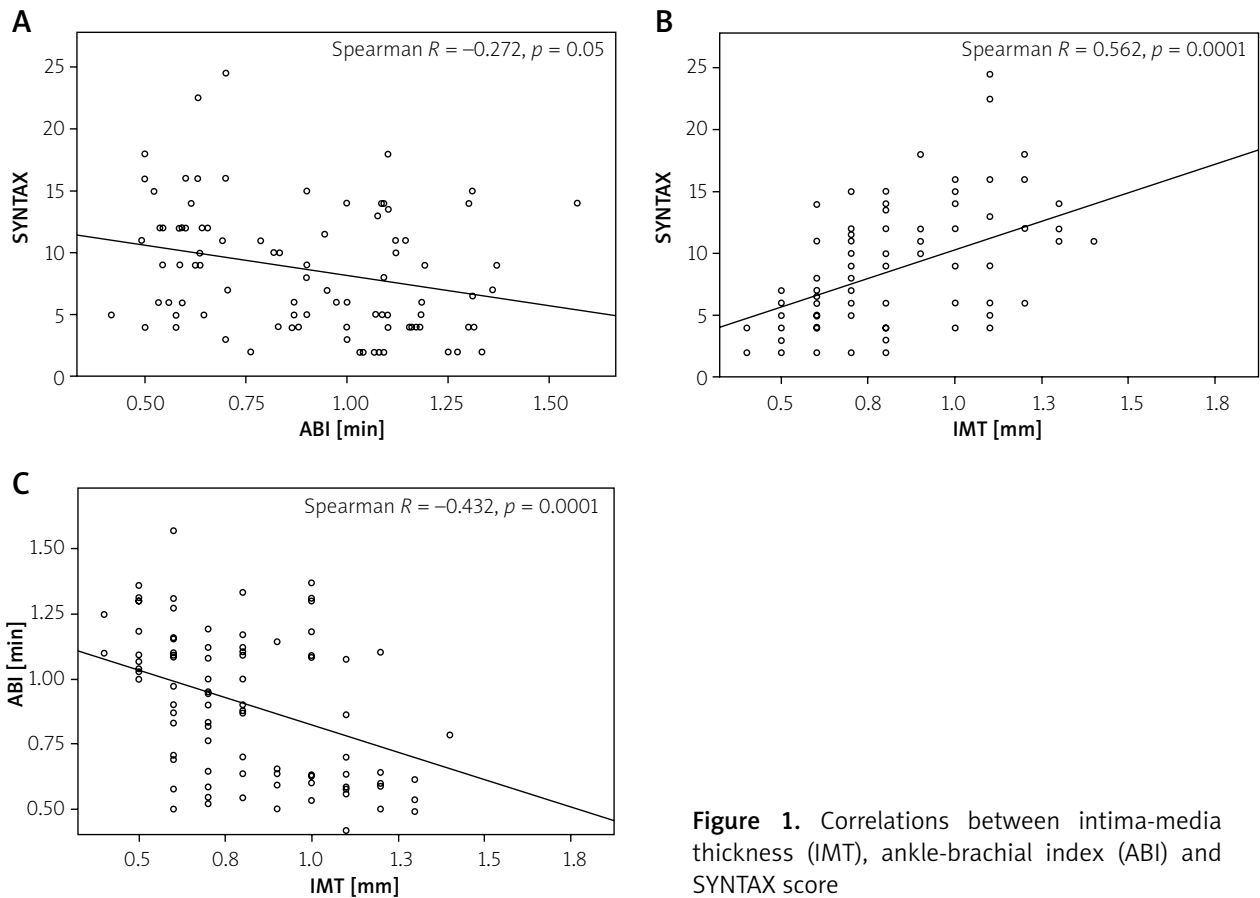


Figure 1. Correlations between intima-media thickness (IMT), ankle-brachial index (ABI) and SYNTAX score

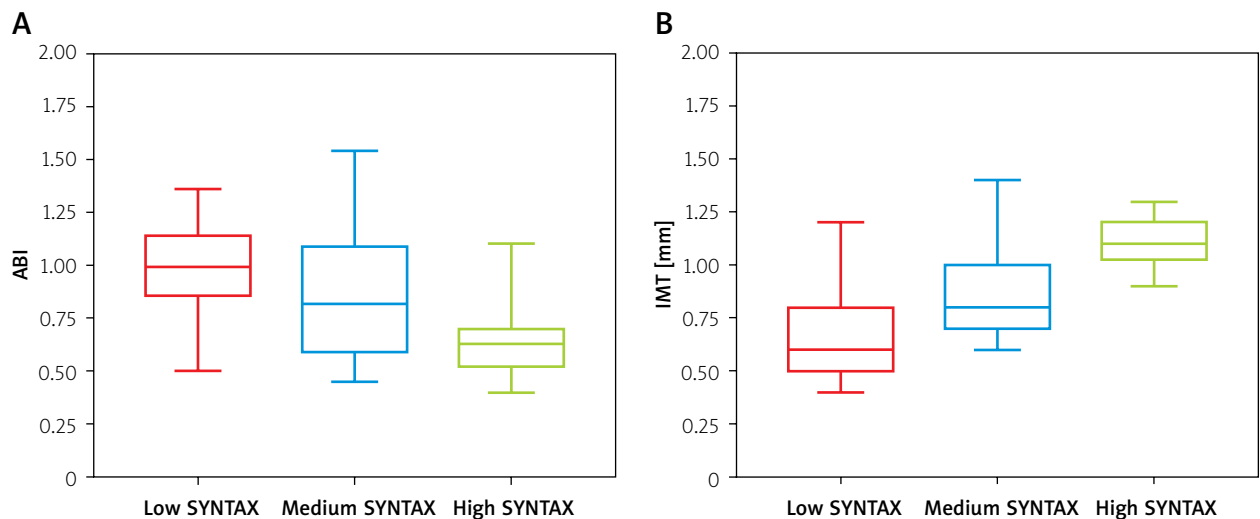


Figure 2. Ankle-brachial index (ABI) (**A**) and intima-media thickness (IMT) (**B**) for low (0–4 points), medium (5–11 points) and high SYNTAX score (12 points and more). Means for low SYNTAX score were 1 ± 0.2 for ABI and 0.7 ± 0.3 mm for IMT; for medium SYNTAX score were 0.9 ± 0.3 for ABI and 0.9 ± 0.2 mm for IMT; for high SYNTAX score were 0.7 ± 0.2 for ABI and 1.1 ± 0.1 mm for IMT. Markings on the graphs outside box plots represent outliers. Box shows range from first to third quartile. Whiskers show maximal and minimal non-outlier values. The vertical line in the box plot shows the median. All results were significant with $p < 0.001$ for IMT and $p = 0.006$ for ABI

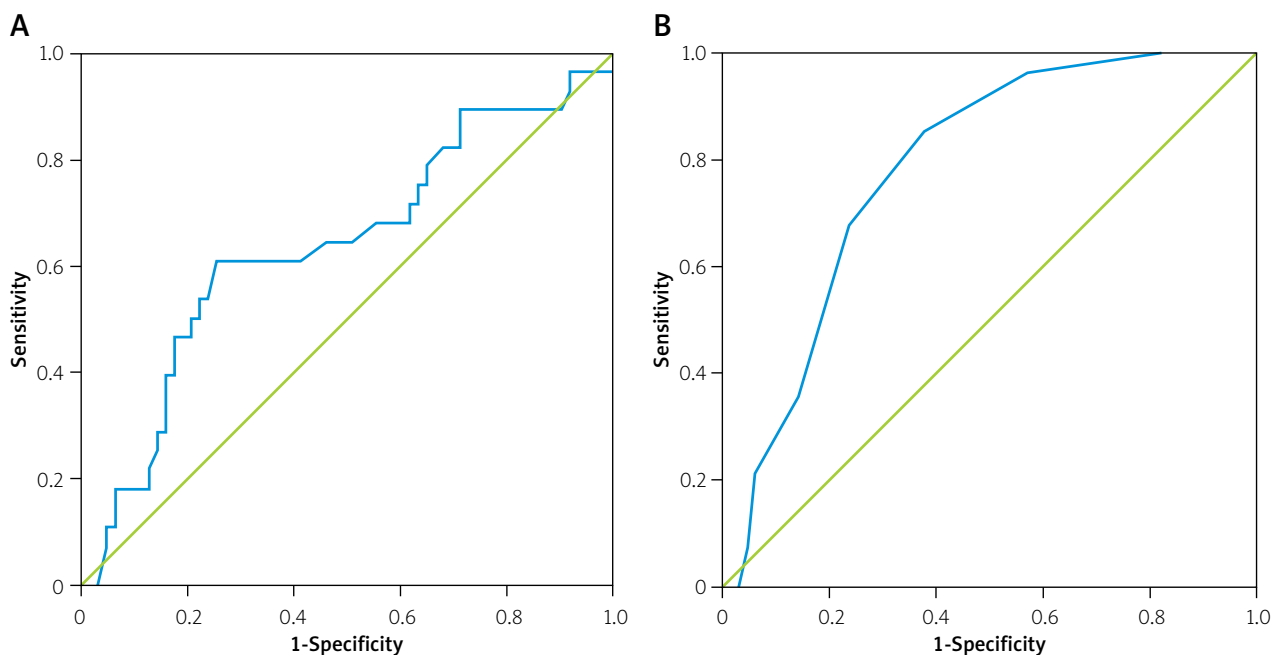


Figure 3. Receiver operating characteristics (ROC) curves for ankle-brachial index (ABI) (A), intima-media thickness (IMT) (B) and SYNTAX score. A high-risk score was defined as a SYNTAX score of 12 points or more

22–25]. However, the majority of them correlated ABI or IMT with SYNTAX score in patients undergoing elective procedures due to stable angina. Thus, the relationship between SYNTAX score and PAD in patients presenting with MI remains widely unexplored. Our study provides some additional insights into CAD complexity as measured by the SYNTAX score in patients presenting with MI and advanced PAD.

One of the main advantages of ABI is its simplicity and high availability. In our study patients with lower ABI had higher a SYNTAX score. This result is consistent with other studies. Sebastiani *et al.* [10] observed that patients with ABI < 0.9 (PAD group) had about a 70% higher mean SYNTAX score (17.6 points) than patients in the normal ABI group (ABI 1.0 to 1.4). Similarly, Korkmaz *et al.* [22] assessed 150 patients with non-ST-segment elevation acute coronary syndrome undergoing coronary angiography and correlated ABI with SYNTAX score. They observed the highest SYNTAX score in the PAD group. Likewise, in our study, after dividing patients into SYNTAX tertiles, the lowest ABI was observed in the highest SYNTAX group.

When comparing three groups with low, medium and high SYNTAX scores, we observed a significant difference in IMT. Accordingly, Korkmaz *et al.* [12] divided patients into two groups with a SYNTAX score < and > 16. Patients with a SYNTAX score > 16 had significantly greater IMT. These results are comparable to other studies where carotid artery remodeling and complex atherosclerotic plaques in carotid arteries were positively associated with atherosclerosis in coronary arteries [26, 27]. Of note, a cardiovascular magnetic resonance study reported that

patients with more advanced CAD had a higher prevalence of lipid-rich necrotic core in carotid arteries [28]. Moreover, the study presented by Aslan *et al.* showed that patients with three-vessel CAD, as compared to one-vessel disease, had the highest carotid stiffness, fibrinogen and hs-CRP levels [6]. Notably, IMT is associated not only with CAD but also with pan-vascular atherosclerosis. Wrotniak *et al.* in their recent study observed that IMT > 1.3 mm was an independent predictor of multi-territorial atherosclerosis [29].

We evaluated both IMT and ABI to assess whether the combination of these two measurements may predict SYNTAX score as precisely as each modality alone. We used the grouping method proposed by Ikeda *et al.* [16], who used the definition from the PARTNERS program for ABI [30]. Ikeda *et al.* reported that the highest mean SYNTAX score was observed in patients with the lowest ABI and highest IMT. Similarly, we found significant differences between groups, and the highest ones were observed between groups A (normal ABI and IMT) and D (low ABI and high IMT), where we noted almost a two-fold difference between the groups.

Our study showed that patients with PAD measured by ABI or IMT had substantially higher troponin levels on admission. Our work adds to the body of findings that patients with PAD have greater myocardium at risk, as patients with higher troponin levels were found to have higher mortality rates [31]. Our findings show that patients with PAD may have more extensive MI, which may be explained by more complex CAD.

Finally, using ROC curves, we confirmed that both IMT and ABI might predict high SYNTAX score, but IMT has

greater specificity and sensitivity. These findings are in line with the study from Ikeda *et al.* [32]. However, that study used automatic carotid IMT measurement and was not limited to patients with MI.

Our study has some limitations. First of all, our design was observational. Moreover, our study population is relatively small, and there was no clinical follow-up. Further, although we found significant differences between SYNTAX score, ABI and IMT, we observed overlap in IMT and ABI between the 3 groups of SYNTAX score. It is highly probable that with a greater study population the overlap could be reduced. Lastly, the SYNTAX score was measured during acute MI although it was created to be used in stable CAD and has some limitations when used in patients with AMI. There are several ways to calculate the SYNTAX score in acute MI [33–35], such as residual SYNTAX score, baseline SYNTAX score (pre-wiring) or measuring the SYNTAX score after wiring IRA. We decided to use the latter method, as it should have given us the nearest possible SYNTAX score not only during the acute phase but also just before acute MI.

Conclusions

Our study showed that both IMT and ABI are correlated with SYNTAX score (positively for IMT and negatively for ABI). We found that combining both IMT and ABI in patients with MI is also feasible to predict the SYNTAX score. In our study, IMT was responsible for better prediction of the SYNTAX score than ABI. Finally, we showed that the correlation between PAD and extent of CAD is not limited to stable angina patients, but also applies to patients presenting with AMI. Our study confirms that the higher rate of cardiovascular events in patients with PAD presenting with MI may be partially explained by greater coronary lesion complexity. Patients with PAD may present with more complex lesions and more extensive MI. Thus, this group of patients may be more likely to benefit from more highly potent antiplatelet and lipid-lowering therapy.

Conflict of interest

The authors declare no conflict of interest.

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