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ORIGINAL ARTICLE

Low ankle–brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events

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Summary. *Background:* Low ankle–brachial Index (ABI) identifies patients with symptomatic and asymptomatic peripheral arterial disease. The aim of this study was to correlate ABI value (normal or low) with 1-year clinical outcome in patients hospitalized for acute coronary syndromes or cerebrovascular diseases (CVD). *Methods:* ABI was measured in consecutive patients hospitalized because of acute myocardial infarction, unstable angina, stroke or transient ischemic attack (TIA). An ABI lower than or equal to 0.90 was considered abnormal. The primary outcome of the study was the composite of non-fatal acute myocardial infarction, non-fatal ischemic stroke, and death from any cause during the year following the index event. *Results:* An abnormal ABI was found in 27.2% of 1003 patients with acute coronary syndromes, and in 33.5% of 755 patients with acute CVD. After a median follow-up of 372 days, the frequency of the primary outcome was 10.8% (57/526) in patients with abnormal ABI and 5.9% (73/1232) in patients with normal ABI [odds ratio (OR) 1.96; 95% CI 1.36–2.81]. Death was more common in patients with abnormal ABI (OR 2.05; 95% CI 1.31–3.22). Cardiovascular mortality accounted for 81.7% of overall mortality. ABI was predictive of adverse outcome after adjustment for vascular risk factors in the logistic regression analysis (OR 1.93; 95% CI 1.24–3.01). The predictive value of ABI was mainly accounted for by patients hospitalized for acute coronary syndromes (adverse outcome: 12.8% in patients with abnormal ABI and 5.9% in patients with normal ABI, OR 2.35; 95% CI 1.47–3.76). *Conclusions:* An abnormal ABI can be found in one-third of patients hospitalized for acute coronary or cerebrovascular events and is a predictor of an adverse 1-year outcome.

Keywords: acute myocardial infarction, ankle–brachial index, atherosclerosis, stroke, transient ischemic attack, unstable angina.

Patients who have experienced acute coronary syndromes, such as acute myocardial infarction (AMI) or unstable angina (UA), or cerebrovascular events of ischemic origin, such as stroke or transient ischemic attack (TIA), are at high risk for subsequent fatal and non-fatal cardiovascular events [1–4]. It has been consistently reported that the presence of peripheral arterial disease in patients with coronary artery disease (CAD) or cerebrovascular disease (CVD) increases the risk for both early [5,6] and late cardiovascular events [7–9].

Atherosclerosis of the lower limbs can be reliably detected by the ankle–brachial index (ABI). Only a minority of patients with a low ABI (≤ 0.9) have intermittent claudication or are symptomatic [10,11]. A low ABI is associated with an unfavorable cardiovascular long-term outcome in patients with both clinical and subclinical peripheral arterial disease [12,13].

Limited information [14,15] is available on the incidence of low ABI in patients admitted to hospital with acute cardiovascular events and on whether an abnormal ABI in these patients is a predictor of short-term adverse outcome. The aim of the present study was to assess the incidence of abnormal ABI in patients hospitalized for an acute coronary or cerebrovascular event and to prospectively evaluate the 1-year outcome of these patients with respect to normal or abnormal ABI. The study outcome included non-fatal AMI, non-fatal ischemic stroke (IS), and death from any cause.

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[1]See Appendix.

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Methods

Patients

Patients of both genders and any age, admitted to hospital for the first episode or recurrence of either acute coronary syndromes (AMI or UA) or cerebrovascular ischemic events of atherothrombotic origin (stroke or TIA) were included in the study. Patients with a life-expectancy of less than 6 months were excluded from the study. Inclusion of consecutive patients was secured by the use of screening log-books. The diagnosis of the qualifying event relied on the criteria used by the individual participating study centers. Patients with CVD of cardioembolic origin (i.e. patients with atrial fibrillation or intracardiac thrombi) were excluded from the study, as were those with hemorrhagic stroke. Patients provided written informed consent.

Study design

The Polyvascular ATHerothrombosis Observational Survey (PATHOS) was a prospective, cohort study with the aim of evaluating the incidence of abnormal ABI (in patients presenting with an acute coronary or cerebrovascular event) and the 1-year outcome in patients with normal or abnormal ABI. The study was performed in 49 Italian centers (24 cardiology, 15 neurology and 10 internal medicine departments).

Patients were followed-up for at least 12 months in order to assess cardiovascular recurrences and mortality. The study protocol was approved by the institutional review board of the participating hospitals.

Baseline measurements

Cardiovascular risk factors and clinical features of the qualifying event were recorded at baseline, and medical treatment was recorded at discharge. Cardiovascular risk factors included previous ischemic events, diabetes mellitus, hypertension, smoking habit, hyperlipidemia, heavy alcohol consumption, and excess bw. Fasting glucose and lipid profile as well as blood pressure were recorded at hospital discharge. Relevant comorbidities that could influence the outcome were also recorded. ABI measurement was performed during the hospital stay. The presence of intermittent claudication in the study population was assessed by means of an updated version of the San Diego Claudication Questionnaire [16].

ABI measurement

ABI was calculated according to McDermott [17] by measuring the systolic blood pressure from both the right and left brachial arteries, the right and left posterior tibial arteries and the dorsalis pedis arteries while the patient was supine. ABI was determined by qualified personnel whose ability was certified during specific training sessions [18]. Appropriately sized cuffs were used. Systolic pressure was detected with a hand-held 8-MHz Doppler probe (D900; Huntleigh, UK). The ABI was calculated as the ratio between the higher of the systolic blood pressures at the anterior or posterior tibial artery in the right or in the left ankle, and the systolic pressure in the corresponding right or left arm. ABI was considered abnormal if it was lower than or equal to 0.90 at least on one side. Patients were categorized according to ABI values: ≤ 0.90 (abnormal), or > 0.90.

Outcome measures

The primary outcomes of the study were non-fatal AMI, non-fatal IS, and death from any cause, during a study period of at least 1 year from the index event. For adjudication purposes, non-fatal AMI was defined as the presence of symptoms consistent with the World Health Organization criteria [19], associated with abnormal levels of necrosis markers (including troponin) or diagnostic electrocardiogram (ECG) changes. IS was defined as the presence of a new focal neurologic deficit lasting for more than 24 h. Computerized tomography or magnetic resonance images were required to exclude the non-ischemic origin of the neurologic event. Death from MI or stroke, or sudden otherwise unexplained death, were considered to be vascular deaths. All outcome events and deaths were reviewed centrally on the basis of clinical records and death certificates by an independent Validation Committee, whose members were unaware of the results of ABI measurements.

Follow-up

Follow-up visits were scheduled at 6 and 12 months from study inclusion. During the follow-up visits, patients were asked about hospitalization occurring since the previous visit and underwent clinical and instrumental evaluation when necessary. Patients who did not attend follow-up were called by telephone and asked about their health and the occurrence of recurrent MI or stroke. For patients with outcome events, the clinical records were collected. Date and cause of death were recorded for patients who died during the study.

Statistical analysis

All enrolled patients hospitalized for acute cerebrovascular events or acute coronary syndromes who survived the acute episode were included in the analysis. Demographic data and clinical features were analyzed using descriptive methods. Quantitative variables were summarized using mean, standard deviation, minimum, median and maximum. Categorical variables were summarized by counts and percentages.

The proportion of patients with abnormal ABI and their 95% CIs were estimated according to the location (cerebrovascular or coronary) of the qualifying event and overall.

The association between the occurrence of study outcome (non-fatal MI, non-fatal stroke, or death) and ABI status (abnormal/normal) stratified by type of qualifying event (AMI, UA, IS, TIA) and location (CVD, CAD) was assessed by the

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Cochran–Mantel–Haenszel test. The homogeneity of the odds ratios (ORs) across strata was tested by the Breslow-Day test. Common ORs and their 95% CIs were also calculated.

As explorative analysis, a logistic regression model (with a backward approach) was carried out to assess the relationship between the study outcome and the following covariates: ABI status, age, gender, smoking habit, diabetes mellitus, hypertension, total cholesterol, new Q-wave at ECG, ejection fraction, life-threatening arrhythmias, ST segment abnormalities, residual ischemia, troponin elevations, carotid origin TIA, vertebrobasiliar origin TIA, and type of stroke according to TOAST classification (atherosclerosis of main arteries and occlusion of small vessels and IS with cause not determined) [20]. All these covariates were included in the model as dichotomous variables, except for age (continuous).

Time to first event and time to death (in days) were defined as the time from the date of the qualifying event and the date of the first event or the date of death, respectively. Survival curves for patients with abnormal or normal ABI were estimated using the Kaplan–Meier method and compared by the log-rank test.

SAS system version 8.2 for WINDOWS was used to perform the statistical analysis. All statistical tests were two-tailed with $\alpha = 0.05$.

The sample size of the study was driven by the number of patients found to have an abnormal ABI. Recruitment was stopped once an incidence of abnormal ABI of about 30% was observed that was stable over patient accrual. This incidence was estimated to allow the definition of two patient groups (normal or abnormal ABI) large enough to show a difference of 30–50% in the absolute risk of outcome events for an estimated 1-year overall rate not lower than 6%.

Results

Study population

One thousand seven hundred and sixty-nine consecutive patients were included in the study. Eleven patients were not included in the analysis because they died during the hospital stay as a direct consequence of the initial event (stroke or MI). Of the 1758 included in the analysis, 1003 were hospitalized for acute coronary syndromes [633 AMI (36.0%) and 370 UA (21.0%)] and 755 for acute CVD [502 stroke (28.6%) and 253 TIA (14.4%)]. Demographic and clinical characteristics of patients with normal and abnormal ABI are shown in Table 1, and treatments at hospital discharge are shown in Table 2. On the basis of 1708 evaluable Claudication Questionnaires, 155 patients (9.1%), 101 with an acute coronary syndrome and 54 with an acute CVD as qualifying event, complained of symptoms of peripheral arterial disease.

ABI results

An abnormal ABI was found in 526 patients (29.9%; 95% CI 27.8–32.1): 273 (27.2%) with acute coronary syndromes, and

Table 1 Baseline characteristics of the patients with abnormal or normal ankle–brachial index (ABI)

	ABI > 0.9, $n = 1.232$	ABI ≤ 0.9, $n = 526$	Total, $n = 1.758$	*P*-value
Female sex, no. (%)	359 (29.1)	173 (32.9)	532 (30.3)	
Caucasian race, no. (%)	1.228 (99.7)	526 (100)	1.754 (99.8)	
Age (years)	65.1 ± 12	70.2 ± 10.8	66.6 ± 11.9	< 0.0001
Body mass index (kg m^{-2})	26.9 ± 3.9	26.7 ± 4.4	26.8 ± 4.1	
Smoking (current), no. (%)	130 (25.0)	130 (27.4)	438 (24.9)	
Heavy alcohol consumption, no. (%)	7.4 (6.0)	24 (4.6)	98 (5.6)	
Total cholesterol ≥ 240 mg dL^{-1}, no. (%)	220 (17.9)	93 (17.7)	313 (17.8)	
Low HDL cholesterol (< 40 mg dL^{-1}), no. (%)	359 (29.1)	186 (35.4)	545 (31.0)	0.035
High LDL cholesterol (≥ 130 mg dL^{-1}), no. (%)	439 (35.6)	188 (55.7)	627 (35.7)	
High triglycerides (≥ 150 mg dL^{-1}), no. (%)	385 (31.3)	177 (33.7)	562 (32.0)	

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Therapies at discharge according to qualifying event and ankle–brachial index (ABI) status

	Cerebrovascular disease, no. (%)	Coronary artery disease, no. (%)	ABI normal, no. (%)	ABI abnormal, no. (%)	*P*
Nitrates	62 (8.2)	631 (62.5)	477 (38.7)	21.3 (40.1)	
Diuretics	128 (16.9)	291 (28.8)	259 (21.0)	157 (29.8)	< 0.001
AIRA	45 (5.9)	38 (3.8)	52 (4.2)	31 (5.9)	
Calcium antagonists	233 (30.7)	280 (21.7)	338 (27.4)	174 (33.1)	0.02
ACE inhibitors	328 (43.2)	664 (65.0)	684 (55.5)	305 (58.0)	
Beta-blockers	69 (9.1)	655 (64.9)	536 (43.5)	188 (35.7)	0.002
Antiplatelet agents	701 (92.4)	932 (92.3)	1.145 (92.9)	483 (91.8)	
Glucose-lowering drugs*	165 (21.7)	170 (16.8)	205 (16.7)	128 (24.3)	0.01
Statins	125 (16.5)	575 (56.9)	511 (41.5)	188 (35.7)	0.02

*Including insulin.

AIRA, angiotensin-receptor antagonist; ACE, angiotensin-converting enzyme.

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253 patients (33.5%) with acute CVD. The proportions of abnormal ABI values in patients with AMI and UA were 24.5% and 31.9%, respectively. The proportions of abnormal ABI values in patients with stroke and TIA were 34.7% and 31.2%, respectively. Nine of the 11 patients excluded from the analysis because they died as a consequence of the initial event had an abnormal ABI.

The two cohorts of patients with abnormal and normal ABI were different with regard to age, high-density lipoprotein cholesterol, incidence of diabetes, hypertension, history of IS, heart failure, and carotid artery revascularization. Administration of diuretics, calcium antagonists, beta-blockers, glucose-lowering agents and statins was more common in patients with normal ABI.

ABI and clinical outcome

Sixty-six patients did not fully adhere to the follow-up program, but phone calls allowed the collection of outcome data. Therefore, these 66 patients were included in the outcome analysis, and the follow-up was completed for the entire population.

The median follow-up period was 372 days, and was similar in patients with acute coronary syndromes and in patients with acute CVD. Of the 142 reported outcome events, 134 occurring in 130 patients (7.4%) were validated by the external adjudication committee. Fifty-seven of 526 patients with abnormal ABI (10.8%) had an outcome event as compared to 73 of 1232 (5.9%) patients with normal ABI (OR 1.96; 95% CI 1.36–2.81). The frequency of vascular death was 5.9% in patients with abnormal ABI and 2.9% in those with normal ABI (OR 2.14; 95% CI 1.31–3.50). Death from any cause occurred in 7.0% of patients with abnormal ABI and in 3.7% of those with normal ABI (OR 2.05; 95% CI 1.31–3.22).

Among patients hospitalized for acute CAD, 35 of the 273 patients (12.8%) with abnormal ABI experienced an outcome event, compared with 43 of the 730 (5.9%) patients with normal ABI (OR 2.35; 95% CI 1.47–3.76). Among patients hospitalized for acute CVD, 22 of the 253 (8.7%) with abnormal ABI presented an outcome event, compared with 30 of the 502 (6.0%) with normal ABI (OR 1.50; 95% CI 0.85–2.66) (Fig. 1). In Table 3, each component of the composite outcome is reported according to the ABI value and the cardiovascular or cerebrovascular status. One patient experiencing a non-fatal vascular event as the first occurring outcome event eventually died from a cardiovascular event.

The ORs for cardiovascular events in each of the four clinical groups are reported in Fig. 1. The ORs were found to be consistent across the two clinical presentations of acute CAD (AMI, OR 2.40, 95% CI 1.18–3.87; and UA, OR 2.91, 95% CI 1.32–6.64). The OR for cardiovascular events in patients presenting with stroke was 1.02 (95% CI 0.52–2.00), and the OR for patients presenting with TIA was 4.79 (95% CI 1.40–16.41). There was no heterogeneity among patients presenting with CAD and CVD (Breslow Day Test, $P = 0.0751$).

The linear association between ABI reduction and outcome events after adjusting for clinical groups was statistically significant (Cochran–Mantel–Haenszel $\chi^2 = 24.41$; $P < 0.001$). Patients with a very low ABI (< 0.60) and a low ABI (between 0.60 and 0.90) had a higher incidence of outcome events: ORs 4.08 (95% CI 2.34–7.12) and 1.55 (95% CI 1.03–2.33), respectively.

The time course to outcome event is shown in Fig. 2. Both the cumulative incidence of composite outcome and death were higher in patients with abnormal ABI for any outcome event (log-rank test = 30.38, $P < 0.0001$) and for death (log-rank test = 18.86, $P < 0.0001$). Irrespective of the ABI value, the presence of typical peripheral arterial disease symptoms was associated with an adverse outcome (OR 1.86; 95% CI 1.29–2.67).

At multivariate analysis, ABI was predictive of adverse outcome after adjustment for vascular risk factors in the logistic regression (OR 1.93; 95% CI 1.24–3.01, $P = 0.0034$). Other significant risk factors were as follows: increasing age ($P < 0.0001$), life-threatening arrhythmias ($P < 0.0001$), ejection fraction ≤ 35% ($P = 0.0106$), large artery atherothrombotic stroke ($P = 0.0297$) and ST segment abnormalities ($P = 0.0298$).

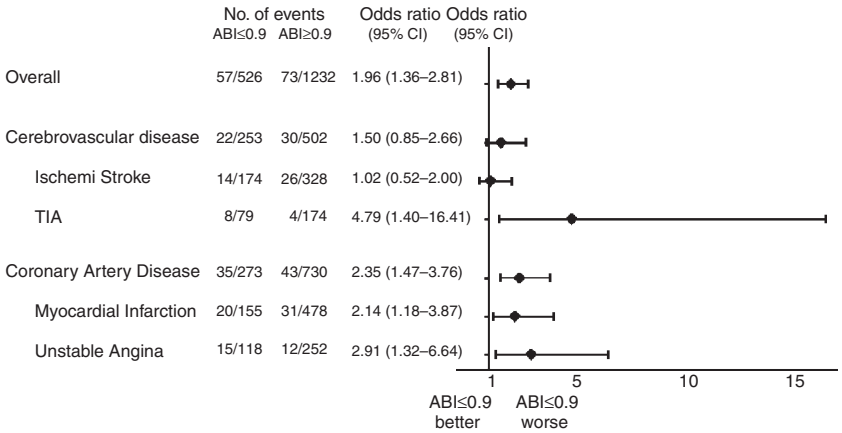

Fig. 1. Outcome events according to ankle–brachial index (ABI) values (≤OR 7 to 0.9) in the overall study population and in each individual group.

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Table 3 Individual components of the outcome event reported according to the ankle–brachial index (ABI) value in coronary artery disease and cerebrovascular disease

Patients	Event	ABI ≥ 0.9, *n* (%)	ABI > 0.9, *n* (%)	Total, *n* (%)	Odds ratio	95% CI	
						Lower	Upper
Cerebrovascular disease ($n = 755$)	Non-fatal AMI	1 (0.4)	3 (0.6)	4 (0.5)	0.66	0.07	6.38
	Non-fatal stroke	8 (3.2)	12 (2.4)	20 (2.6)	1.33	0.54	3.30
	Vascular death	11 (4.3)	13 (2.6)	24 (3.2)	1.71	0.75	3.87
	All deaths	13 (5.1)	16 (3.2)	29 (3.8)	1.65	0.78	3.48
	Any event	22 (8.7)	30 (6.0)	52 (6.9)	1.50	0.85	2.66
Coronary artery disease ($n = 1003$)	Non-fatal AMI	10 (3.7)	11 (1.5)	21 (2.1)	2.49	1.04	5.92
	Non-fatal stroke	2 (0.7)	3 (0.4)	5 (0.5)	1.79	0.30	10.8
	Vascular death	20 (7.3)	23 (3.2)	43 (4.3)	2.43	1.31	4.50
	All deaths	24 (8.8)	29 (4.0)	53 (5.3)	2.33	1.33	4.08
	Any event	35 (12.8)	43 (5.9)	78 (7.8)	2.35	1.47	3.76
Total population ($n = 1758$)	Non-fatal AMI	11 (2.1)	14 (1.1)	25 (1.4)	2.03	0.91	4.52
	Non-fatal stroke	10 (1.9)	15 (1.2)	25 (1.4)	1.41	0.63	3.18
	Vascular death	31 (5.9)	36 (2.9)	67 (3.8)	2.14	1.31	3.50
	All deaths	37 (7.0)	45 (3.7)	82 (4.7)	2.05	1.31	3.22
	Any event	57 (10.8)	73 (5.9)	130 (7.4)	1.96	1.36	2.81

AMI, acute myocardial infarction; CI, confidence interval.

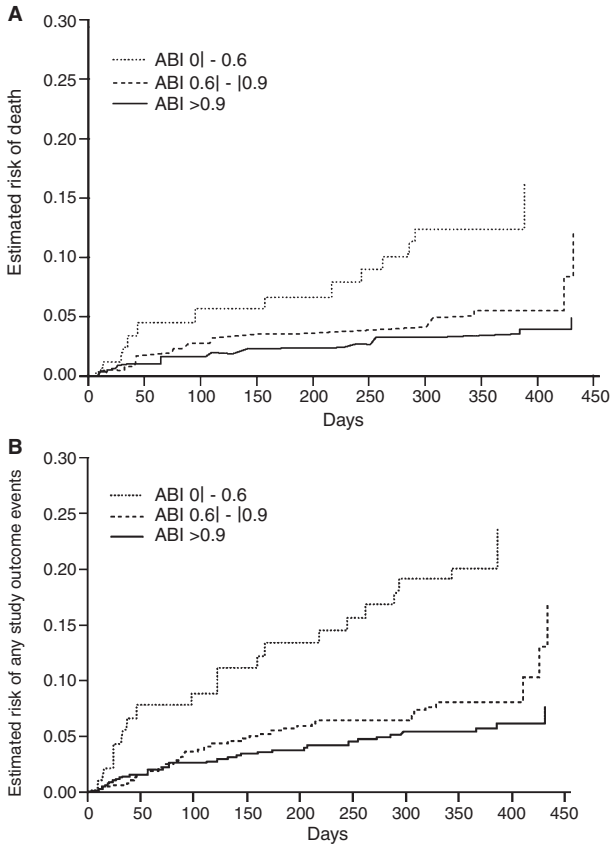

Fig. 2. Estimated cumulative risk of death (Panel A) and risk of any study outcome events (Panel B) in patients according to low ankle–brachial Index levels. (A) Death from any cause. (B) Combined study outcome events.

Discussion

This study indicates that an abnormal ABI is an independent risk factor for an adverse outcome in patients hospitalized for acute coronary syndromes or cerebrovascular events. The frequencies of cardiovascular events and death were significantly higher in patients with abnormal ABI than in patients with normal ABI. This difference was shown to be present as early as at the first year from hospitalization. Death was the most frequent of the outcome events. Cardiovascular mortality accounted for 81.7% of the overall mortality. The high rate of abnormal ABI, nearly 30% in a large cohort of patients with acute CAD or cerebrovascular events, underlines its clinical value.

ABI is an easy-to-perform, inexpensive test that is feasible with the medical equipment available in most wards. ABI has traditionally been used as a diagnostic and prognostic tool for the management of patients with peripheral artery disease. Earlier studies have shown that in the assessment of primary risk, an abnormal ABI is a predictor of cardiovascular events in the long term [13,21–23]. A more recent study has shown that in patients at high risk or those who have had a previous vascular event, both clinically overt peripheral arterial disease and an abnormal ABI are associated with an unfavorable outcome after a period of 4.5 years [24]. There are only few data suggesting that symptomatic peripheral arterial disease [5,6] or an abnormal ABI [14,15] are short-term prognostic factors of adverse outcome. We observed an early divergence of the cumulative incidence curves of patients with normal or abnormal ABI. Indeed, the difference in mortality between these two groups was statistically significant within 1 year from hospitalization. It is noteworthy that this early difference was seen despite the exclusion from the analysis of the nine patients with abnormal ABI who died as a consequence of the initial event.

A clinical history of peripheral arterial disease and typical leg symptoms identified only 20% of the population at risk discovered by ABI.

The incidence of abnormal ABI was higher in patients presenting with acute cerebrovascular events than in patients

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presenting with acute coronary syndromes, probably due to their older age [25]. The predictive value of abnormal ABI for cardiovascular events and death did not show significant heterogeneity between CAD and CVD patients. However, the prognostic role of ABI was higher in patients hospitalized for coronary artery events than in those hospitalized for cerebrovascular events. The uncertain predictive value of ABI in patients presenting with CVD deserves some comment. Stroke is a disease of composite etiology, and it is unlikely that ABI, a marker of systemic atherosclerosis, could be predictive of recurrence after a stroke because of cardioembolism or small vessel disease. Indeed, even in the assessment of primary risk, the role of ABI as predictor of cerebrovascular events remains controversial [22,26,27]. Furthermore, the 1-year mortality of stroke patients is mainly related to the index event, whereas their long-term outcome is probably related to systemic atherosclerosis [28]. The short duration of the follow-up period (1 year) of our study could have precluded a true estimate of the prognostic value of ABI in stroke patients. Finally, differences in treatment intensity could be an additional explanation for the different results in patients with acute coronary syndromes or acute CVD.

In this study, an abnormal ABI was found to be a predictor for the composite endpoint of non-fatal vascular events and mortality independently of the established risk factors and organ-specific risk indicators such as low left ventricular ejection fraction in patients with acute coronary syndromes. Whether the association between abnormal ABI and adverse outcome is explained by an overall greater atherosclerotic burden, greater inflammation, inadequate management of risk factors, or all of these together, remains to be elucidated.

Several new markers of primary and secondary cardiovascular risk have recently been proposed [29]. Among these, C-reactive protein seems to be the most interesting candidate for secondary risk stratification for adverse outcome in patients with coronary syndromes and CVD, although recent data bring into question its role as a powerful predictor of risk [30–33]. ABI and C-reactive protein are expressions of different processes in terms of pathophysiology, ABI being a marker of widespread atherosclerosis [34–36], and C-reactive protein indicating plaque destabilization [37]. The two markers could provide additional information when measured in the same patients [38].

Our study, like other observational studies, certainly has some limitations, such as the non-standardized treatment of patients. However, it should be mentioned that, consistent with the current guidelines, most of the patients had more than three treatments. The somewhat lower than expected incidence of non-fatal events could have been a consequence of this extensive therapeutic approach. However, our study also has some strengths that are likely to make our results valid. We included consecutive patients, within a well-defined clinical setting. All the clinical events were validated by an independent adjudication committee that was unaware of the ABI results. Mortality accounted for the large majority of the study outcome events.

The clinical benefit from risk stratification of patients who have had acute coronary syndromes or cerebrovascular events has been questioned, because these patients should already receive all preventive interventions according to the treatment guidelines [36]. However, the recommendations in the current guidelines acknowledge that in a number of very high-risk patients, secondary prevention should be more aggressive [39–41].

In conclusion, PATHOS showed that an abnormal ABI could be found in one-third of the patients with acute CAD or CVD, and identifies a population at high risk of fatal and non-fatal cardiovascular events within 1 year, who should be more closely monitored and might become the target of more intensive therapeutic intervention.

Disclosure of Conflict of Interests

This study was supported by a research grant from Sanofi-Aventis, Italy and Bristol–Myers Squibb, Italy.

Appendix

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