# Ankle-Brachial Index and cardiovascular events in atrial fibrillation

## The ARAPACIS Study

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**Summary**

Atrial fibrillation (AF) patients are at high risk for thrombotic and vascular events related to their cardiac arrhythmia and underlying systemic atherosclerosis. Ankle-Brachial Index (ABI) is a non-invasive tool in evaluating systemic atherosclerosis, useful in predicting cardiovascular events in general population; no data are available in AF patients. ARAPACIS is a prospective multicentre observational study performed by the Italian Society of Internal Medicine, analysing association between low ABI (≤ 0.90) and vascular events in NVAF out- or in-patients, enrolled in 136 Italian centres. A total of 2,027 non-valvular AF (NVAF) patients aged > 18 years from both sexes followed for a median time of 34.7 (interquartile range: 22.0–36.0) months, yielding a total of 4,614 patient-years of observation. Mean age was 73 ± 10 years old with 55 % male patients. A total of 176 patients (8.7 %) experienced a vascular event, with a cumulative incidence of 3.81 %/patient-year. ABI≤ 0.90 was more prevalent in patients with a vascular event compared with patients free of vascular events (32.2 vs 20.2 %, p< 0.05). On Cox proportional hazard analysis, ABI≤ 0.90 was an independent predictor of vascular events (hazard ratio (HR): 1.394, 95 % confidence interval (CI): 1.042–1.866; p=0.02), vascular death (HR: 2.047, 95 % CI: 1.255–3.338; p=0.004) and MI (HR: 2.709, 95 % CI: 1.485–5.083; p=0.001). This latter association was also confirmed after excluding patients with previous MI (HR: 2.901, 95 % CI: 1.408–5.990, p=0.004). No association was observed between low ABI and stroke/transient ischaemic attack (p=0.91). In conclusion, low ABI is useful to predict MI and vascular death in NVAF patients and may independently facilitate cardiovascular risk assessment in NVAF patients.

**Keywords**

Atrial fibrillation, ABI, ARAPACIS, myocardial infarction, vascular events

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## Introduction

Atrial fibrillation (AF) is associated with a high risk of cardiovascular events and increased morbidity and mortality (1). Cardiovascular events are commonly localised in the cerebral circulation in which AF is responsible for thrombo-embolic stroke (1, 2), but patients with AF frequently suffer from vascular events such as myocardial infarction (MI) indicating that this cardiac arrhythmia is often associated with systemic atherosclerosis (3, 4). Indeed, patients with AF commonly have associated risk factors for atherothrombosis, including hypertension, diabetes mellitus and dyslipidaemia (5, 6). Evidence of systemic atherosclerosis is also associated with AF, as represented by aortic plaque assessed by trans-esophageal echocardiography (7).

Peripheral artery disease (PAD) is an established marker of systemic atherosclerosis, which confers a higher risk of MI and stroke (8). The prevalence of PAD in AF is greatly variable, ranging from 4 % to 16 % (9); the reason for such large variability may be dependent on the fact that in AF clinical setting the objective assessment of PAD by the ankle-brachial index (ABI), which is an established tool for diagnosis of PAD (10), has not been fully evaluated and implemented.

ABI is a simple, inexpensive, and non-invasive PAD measurement, which allows us to define the vascular risk in symptomatic and asymptomatic patients (11–14). Recent data from the Atrial fibrillation Registry for Ankle-brachial index Prevalence Assessment-Collaborative Italian Study (ARAPACIS), which is a multicentre registry performed by the Italian Society of Internal Medi-

cine (SIMI), documented that about one fifth of AF patients had a low ABI (≤0.90), suggesting that asymptomatic PAD may be detected in a large number of AF patients (15).

While low ABI has been associated with an increased risk of vascular events in general population (10, 16, 17), no data have been reported in patients with AF. In this analysis, we report the study that has investigated the association between low ABI and vascular events in a large population affected by non-valvular AF (NVAF) prospectively followed-up for approximately three years.

## Methods

ARAPACIS is a multicentre, observational, prospective study held by the SIMI. The methods and baseline data from the ARAPACIS study have previously been published (15, 18). Patient enrollment started October 1, 2010 and continued until October 31, 2012.

Study protocol was approved for the Coordinator Centre (Sapienza-University of Rome) with number 1902/17.06.2010. The study was subsequently registered at ClinicalTrials.gov (Unique identifier: NCT01161251). According to the list of enrolling centres reported in the Appendix, every institution's Ethics Committee approved the study protocol.

This study was conducted in accordance with the EU Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki.

In brief, the registry population comprised 2,027 patients recruited after signing a written informed consent, both as consecutive out- or inpatients from 136 Italian centres belonging to all the three macro-regions (North, Centre, South).

Patients with a diagnosis of NVAF in the preceding 12 months were consecutively enrolled. Exclusion criteria were as follows: (i) acquired or congenital valvular AF, (ii) active cancer or coexistence of disease with life expectancy less than three years and (iii) pregnancy or hyperthyroidism.

Anthropometric data and complete medical history interview were recorded at the baseline visit to detect the presence of cardiovascular risk factor, previous cardio- and cerebrovascular events or other comorbidities. Data on transthoracic echocardiography, such as ejection fraction, atrial and ventricular dimensions were recorded, even if not mandatory. A comprehensive pharmacological history was also collected (18).

Patients were classified according to international guidelines as paroxysmal, persistent or permanent AF (19).

Stroke risk was categorised using $CHA_2DS_2$-VASc score, created by adding 1 point each for the presence of congestive heart failure (HF), hypertension, age from 65 to 74 years, diabetes mellitus, prior MI or peripheral vascular disease, and female sex, and adding 2 points for stroke or transient ischaemic attack (TIA) and age 75 years or older (20).

At baseline, a measurement of upper and lower limbs systolic blood pressure for ABI calculation was performed by linear Doppler probe and a low ABI (defined as a value ≤0.90) was considered as pathological (10, 11). A centralised training meeting, planned in order to make the ABI measurement both reliable and standardised, was organised during study set-up. Training included demonstration of ABI performance in NVAF patients with clear delineation of each step (21).

ABI values were available for 2,013 patients. The remaining 14 patients were evaluated in a single leg and excluded from the analysis (15).

Patient that withdrew their consent for study participation or developed any of the exclusion criteria were removed from the study. In that situation a specifically designed case report form was collected in each patient at the time of censoring. All data were transferred to the web-central database.

### Events definition

The end-point of the follow-up study was to define the incidence of vascular events among the cohort of NVAF patients, based on the presence of low ABI (≤0.90) at study entry. Vascular events included as follows: vascular death, fatal/non fatal MI, fatal/non fatal stroke or TIA.

Death was classified as vascular unless the central adjudication committee (see below) confirmed an unequivocal non-cardiovascular cause of death. Vascular death included the following: sudden death; progressive congestive HF; procedure related death (surgical or percutaneous revascularisation); and presumed cardiovascular deaths (i.e. those for which a non-cardiovascular cause had not been clearly established). Diagnosis of MI was made according to the definition proposed by the ESC/ACCF/AHA/WHF Task Force (20). If a patient died within four weeks of MI, this event was recorded as fatal MI. Ischaemic stroke was determined on clinical manifestations and confirmed by radiological findings (23). Even in this case, if a patient died within four weeks from stroke, this event was classified as fatal.

### Events validation

Data on vascular events were prospectively collected during follow-up in each centre. Details on every vascular event, as well as death certificates, hospital discharge letter, copy of the medical records of hospitalisation, other clinical documentation were obtained from patients, or in case of death, from patients' relatives or general practitioner and were retained in each enrolling centre.

A blinded committee composed by senior professors (see Appendix) adjudicated events. Every evaluator independently defined event and an independent operator combined results from both evaluations for the final adjudication. When the two evaluators agreed, event was adjudicated. Otherwise, whenever the two evaluators were discordant, the event was adjudicated after a collegial discussion among the study Steering Committee.

### Statistical analysis

As previously published (15) the study was initially designed to include 3,000 patients; in October 2012, an interim analysis to assess the prevalence of ABI in the enrolled populations, showed a higher



 

than expected prevalence of low ABI and the Steering Committee decided to interrupt the patient enrollment. The primary endpoint for the study design was the prevalence of low ABI and thus, the sample size was amended to 2,027 patients leading to an expected prevalence of low ABI of 21% with a 95% confidence interval (CI) width of 3.5% (15). This sample size led to a power higher of 99.9% for the secondary endpoints, assuming a vascular event rate of 17% for patients with ABI≤0.90, and 10% for patients with ABI>0.90 (13).

Continuous variables were reported as mean ± SD or as median and interquartile range (IQR) as appropriate. Comparisons between groups of continuous variables were performed by t-test or Mann-Whitney U test. Categorical variables, reported as counts and percentages, were compared by Chi-square test or Fisher's exact test, when cell count was less than five units, corrected by Bonferroni rule for multiple comparisons. Kaplan-Meier curves were built for MI, vascular death and vascular events (as composite endpoint of vascular death, MI, and stroke/TIA) according to the presence of low ABI have been performed. Log-rank test was performed to analyse differences in survival distributors between subgroups. Univariate and multivariate Cox models were used to assess clinically relevant variables and ABI effects on the endpoints. A forward stepwise model selection procedure based on the AIC was used to select the best multivariate regression model. A two-sided p value <0.05 was considered as statistically significant. All analyses were performed using SPSS v. 22 (IBM, Armonk, NY, USA) and R v. 3.0.2 (R development core team, Vienna, Austria).

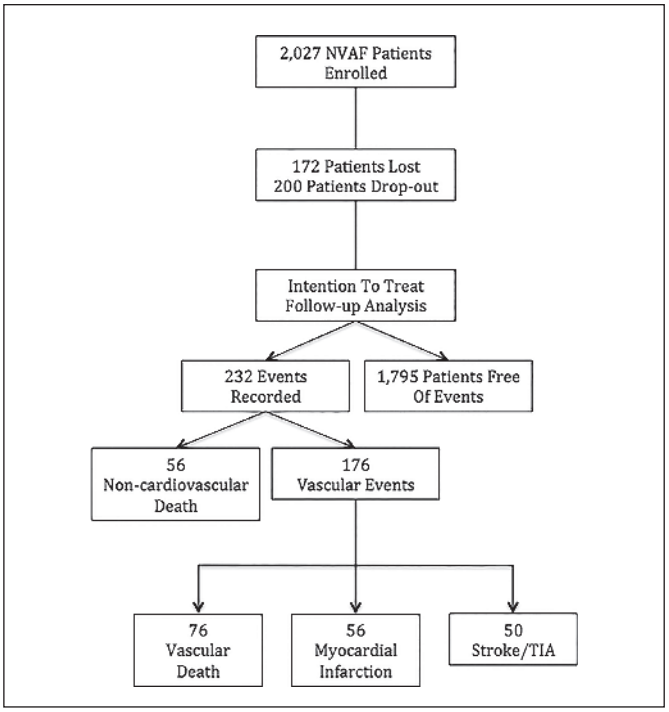


**Figure 1: Flow-chart diagram of patients' study.** The figure shows the composition of study cohort and number of events reported during the follow-up.

## Results

A total of 2,027 patients were enrolled (►Figure 1). Demographic and clinical characteristics of the population have been previously reported (15). Briefly, mean age was 73 ± 10 years, and 55% were males. Permanent NVAF was reported in 44.5% of patients. Among classical cardiovascular risk factors, hypertension was the most often reported (82.5%). Diabetes mellitus was recorded in 23.0% of patients, while dyslipidaemia and smoking habit were reported in 38.5% and 15.0% of patients, respectively. A total of 328 patients (16.2%) experienced a previous MI and 235 patients (11.6%) experienced a previous stroke/TIA. The median (IQR) $CHA_2DS_2$-VASc value was 3 (2–4). Most of the patients (84.4%) had a $CHA_2DS_2$-VASc value ≥2. Regarding antithrombotic therapy, 1, 935 patients (60.7%) were treated with oral anticoagulants (OAC), 389 (19.2%) with antiplatelet agents and 4.5% with both antiplatelet agents and OAC.

### Low ABI and clinical characteristics

Among the overall population, 428 patients (21%) had low ABI (15). ►Table 1 summarises clinical characteristics of patients with ABI≤0.90 and >0.90.

Patients with low ABI were significantly older (p<0.001), more hypertensive (p=0.008) and diabetic (p<0.001) than ones with ABI>0.90.

Previous MI, stroke/TIA and HF more frequently affected clinical history of patients with low ABI than patients with ABI>0.90 (p<0.001).

Accordingly median $CHA_2DS_2$-VASc values were significantly higher in patients with low ABI as well as high thromboembolic risk ($CHA_2DS_2$-VASc≥2) class prevalence (p<0.001).

No significant differences were recorded in pharmacological treatments distribution between the two groups.

### Follow-up and vascular events

All patients were followed for a median time of 34.7 (IQR: 22.0–36.0) months yielding a total of 4,614 patient-years of observation. At follow-up, 232 patients experienced a vascular event or a non-cardiovascular death. One hundred seventy-six patients (3.81 per 100 patient-years) experienced a vascular event, detailed as follows: vascular death (n=70(30% of total events)), MI (n=56(24% of total events)) and stroke/TIA (n=50(22% of total events)).

Fifty-six patients (24% of total events) experienced a non-cardiovascular death.

►Table 2 reports demographic and clinical characteristics of patients who experienced a vascular event. Patients for which a vascular event was recorded were older (p<0.001), with a higher prevalence of HF (p<0.001), higher $CHA_2DS_2$-VASc score (median (IQR): 4(3–5) vs 3(2–4), p<0.001) and a clinical history more frequently complicated by cardiac (p<0.001) and cerebrovascular events (p=0.004) than patients that did not report any event. Thirty-two percent of patients who experienced vascular events had low ABI compared to 20% of patients without vascular events (p<0.05).

**Table 1: Baseline clinical characteristics and pharmacological treatments according to ABI≤0.90 presence***

| | ABI≤0.90 n=428 | ABI>0.90 n=1,585 | P-value |
|---|---|---|---|
| Age, years (mean ± SD) | 77 ± 9 | 72 ± 10 | <0.001† |
| Males, n (%) | 230 (53.7) | 872 (55.0) | 0.63‡ |
| Atrial fibrillation type | | | 0.25‡ |
| Paroxysmal, n (%) | 184 (43.0) | 655 (41.3) | NS§ |
| Persistent, n (%) | 68 (15.9) | 215 (13.6) | NS§ |
| Permanent, n (%) | 176 (41.1) | 715 (45.1) | NS§ |
| Hypertension, n (%) | 372 (86.9) | 1,291 (81.5) | 0.008‡ |
| Diabetes, n (%) | 144 (33.6) | 318 (20.1) | <0.001‡ |
| Previous MI, n (%) | 46 (26.4) | 282 (15.2) | <0.001‡ |
| Previous Stroke/TIA, n (%) | 32 (18.4) | 203 (11.0) | <0.001‡ |
| Heart Failure, n (%) | 55 (31.6) | 357 (19.3) | <0.001‡ |
| $CHA_2DS_2$-VASc#, (median [IQR]) | 4 [3–5] | 3 [2–4] | <0.001¶ |
| $CHA_2DS_2$-VASc# CLASSES | | | <0.001‡ |
| Score 0, n (%) | 6 (1.4) | 73 (4.6) | <0.05§ |
| Score 1, n (%) | 24 (5.6) | 212 (13.4) | <0.05§ |
| Score ≥2, n (%) | 398 (93.0) | 1,300 (82.0) | <0.05§ |
| Concomitant therapies | | | |
| Antithrombotic therapy | | | 0.43‡ |
| None, n (%) | 67 (15.7) | 247 (15.6) | NS§ |
| Antiplatelets, n (%) | 88 (20.6) | 298 (18.8) | NS§ |
| OAC, n (%) | 249 (58.2) | 974 (61.5) | NS§ |
| OAC+Antiplatelets, n (%) | 24 (5.6) | 66 (4.2) | NS§ |
| Statins, n (%) | 170 (39.7) | 560 (35.3) | 0.09‡ |
| Beta-Blockers, n (%) | 165 (38.6) | 652 (41.1) | 0.11‡ |
| ACEIs, n (%) | 164 (38.3) | 543 (34.3) | 0.66‡ |
| ARBs, n (%) | 146 (34.1) | 543 (34.3) | 0.95‡ |
| Calcium Channel Blockers, n (%) | 108 (25.2) | 437 (27.6) | 0.33‡ |

ABI=ankle-brachial index; ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; IQR=interquartile range; MI=myocardial infarction; NS=not significant; OAC=oral anticoagulants; TIA=transient ischaemic attack. *Data about 2,013 patients; †=t-test; ‡= $Chi^2$ test; §=Bonferroni correction; ¶=Mann Whitney U Test.

On Cox proportional hazard analysis, age (hazard ratio (HR): 1.060 (per year), 95% confidence interval (CI): 1.043–1.078; p<0.001), any antithrombotic therapy (HR: 0.495, 95%CI: 0.362–0.675; p<0.001) and low ABI (HR: 1.394, 95%CI: 1.042–1.866; p=0.026) (►Figure 2A) predicted vascular events after adjustment for diabetes mellitus, statins, hypertension, sex, previous cardio- or cerebrovascular events, type of AF and enrolling centre.

Patients who died of vascular death were older (79 ± 8 vs 73 ± 10 years, p<0.001), were more frequently affected by HF (41.4% vs 19.6%, p<0.001), had higher $CHA_2DS_2$-VASc score (median (IQR): 4(3–5) vs 3(2–4), p<0.001) and a higher prevalence of low ABI (38.6% vs 20.6%, p<0.05).

**Table 2: Baseline clinical and demographic characteristics according to vascular events occurrence.**

| | Vascular events n=176 | No vascular events n=1,851 | P-value |
|---|---|---|---|
| Age, years (mean ± SD) | 77±9 | 73±10 | <0.001† |
| Age classes | | | <0.001‡ |
| <65, n (%) | 34(19.3) | 543(29.3) | <0.05§ |
| 65–74, n (%) | 31(17.6) | 461(24.9) | <0.05§ |
| ≥75, n (%) | 111(63.1) | 847(45.8) | <0.05§ |
| Males, n (%) | 95(54.0) | 1,014(54.8) | 0.83‡ |
| Atrial fibrillation type | | | 0.38‡ |
| Paroxysmal, n (%) | 73(41.5) | 769(41.6) | NS§ |
| Persistent, n (%) | 19(10.8) | 265(14.3) | NS§ |
| Permanent, n (%) | 84(47.7) | 817(44.1) | NS§ |
| Hypertension, n (%) | 147(83.5) | 1,526(82.4) | 0.71‡ |
| Dyslipidaemia, n (%) | 78(44.3) | 703(38.0) | 0.09‡ |
| Smoking habit, n (%) | 29(16.5) | 275(14.9) | 0.56‡ |
| Diabetes, n (%) | 45(25.6) | 421(22.7) | 0.39‡ |
| Previous MI, n (%) | 46(26.1) | 282(15.2) | <0.001‡ |
| Previous Stroke/TIA, n (%) | 32(18.2) | 203(11.0) | 0.004‡ |
| Heart Failure, n (%) | 55(31.3) | 357(19.3) | <0.001‡ |
| ABI*, (median [IQR]) | 1.05(0.92–1.20) | 1.07(0.98–1.20) | 0.06# |
| ABI*, n (%) | | | 0.006‡ |
| ≤0.90, n (%) | 56(32.2) | 372(20.2) | <0.05§ |
| 0.91–1.39, n (%) | 99(56.9) | 1,282(69.7) | <0.05§ |
| ≥1.40, n (%) | 19(10.9) | 185(10.1) | NS§ |
| $CHA_2DS_2$-VASc, (median [IQR]) | 4[3–5] | 3[2–4] | <0.001¶ |
| $CHA_2DS_2$-VASc CLASSES | | | <0.001‡ |
| Score 0, n (%) | 2(1.1) | 77(4.2) | NS§ |
| Score 1, n (%) | 8(4.6) | 229(12.4) | <0.05§ |
| Score ≥2, n (%) | 166(94.3) | 1,545(83.5) | <0.05§ |
| Concomitant therapies | | | |
| Antithrombotic therapy | | | 0.002‡ |
| None, n (%) | 43(24.4) | 273(14.8) | <0.05§ |
| Antiplatelets, n (%) | 24(13.6) | 365(19.7) | NS§ |
| OAC, n (%) | 104(59.1) | 1,126(60.8) | NS§ |
| OAC+Antiplatelets, n (%) | 5(2.9) | 87(4.7) | NS§ |
| Statins, n (%) | 67(38.1) | 669(36.1) | 0.61‡ |
| Antiarrhythmics, n (%) | 46(26.1) | 496(26.7) | 0.86‡ |
| Beta-Blockers, n (%) | 65(36.9) | 757(40.9) | 0.30‡ |
| ACEIs, n (%) | 64(36.4) | 651(35.2) | 0.75‡ |
| ARBs, n (%) | 53(30.1) | 638(34.5) | 0.24‡ |
| Calcium Channel Blockers, n (%) | 50(28.4) | 501(27.1) | 0.70‡ |

ABI=ankle-brachial index; ACEIs=angiotensin-converting enzyme inhibitors; ARBs=angiotensin II receptor blockers; BMI=body mass index; IQR=interquartile range; MI=myocardial infarction; NS=not significant; OAC=oral anticoagulants; TIA=transient ischaemic attack. *Data about 2,013 patients; †=t-test; ‡=$Chi^2$ test; §=Bonferroni correction; ¶=Mann Whitney U Test.

On Cox proportional hazard analysis, age (HR: 1.071, 95%CI: 1.038–1.104; p<0.001), history of HF (HR: 2.493, 95%CI: 1.522–4.084; p<0.001), any antithrombotic therapy (HR: 0.406, 95%CI: 0.236–0.697; p=0.001) and low ABI (HR: 2.047, 95%CI: 1.255–3.338; p=0.004) (►Figure 2B), independently predicted vascular death after adjustment for diabetes mellitus, statins, hypertension, sex, previous cerebro- or cardio-vascular events, type of AF and enrolling centre.

Patients who experienced MI during follow-up were older (74 ± 8 vs 73 ± 10 years.p<0.001), had more dyslipidaemia (55.4 vs 38%, p=0.008), had more previous MI (33.9 vs 15.7%, p=<0.001), similar $CHA_2DS_2$-VASc score (median (IQR): 4(3–5) vs 3(2–4), p=0.07) and higher prevalence of low ABI (35.7 vs 20.9%, p=0.02). Twice as many patients (30.4% vs 15.2%, p<0.05) did not receive any antithrombotic drug.

On Cox proportional hazard analysis, low ABI (HR: 2.709, 95%CI: 1.485–5.083; p=0.001) (►Figure 1C) and previous MI (HR: 1.926, 95%CI: 0.834–3.135; p=0.04) independently predicted MI after adjustment for diabetes mellitus, statins, hypertension, sex, previous cerebrovascular events, type of NVAF and enrolling centre.

Such analysis was repeated after excluding patients with a clinical history of previous MI. Among 1,699 patients without a history of MI, 37 (2.2%, 0.97 per 100 patient-years) suffered from MI during the follow-up. Patients who experienced MI during follow-up had demographic and clinical characteristics similar to patients who did not.

Only low ABI discriminated the two groups; 37.8% of patients who experienced MI during follow-up had low ABI respect to 20.1% observed in those who did not (HR: 2.901, 95%CI: 1.408–5.990, p=0.004) (►Figure 2D).

Finally, patients who experienced stroke/TIA during follow-up had similar incidence of low ABI (18.8% vs 21.3%, p=0.91) compared to patients who didn't experience a cerebrovascular event. Low ABI it would not seem to influence the incidence of stroke/TIA in NVAF patients (HR: 1.050, 95%CI: 0.484–2.282, p=0.89).

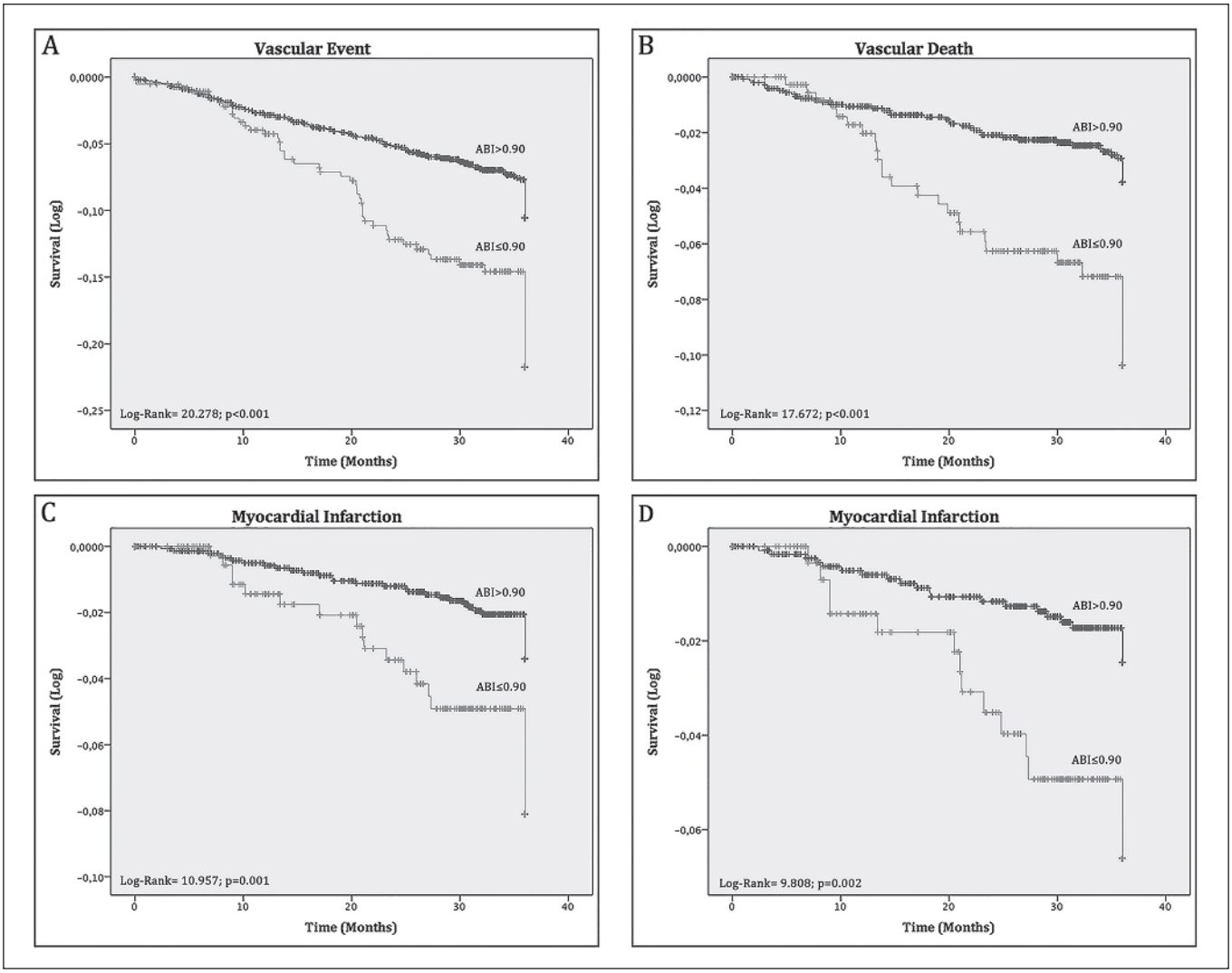


**Figure 2: Comparisons of cumulative incidences between patients with low and normal ABI.** A) Vascular event; B) Vascular death; C) Myocardial infarction; D) Myocardial infarction in patients without previous MI; Survival has been expressed with logarithmic transformation; ABI= ankle-brachial index.

### Sensitivity analysis

In order to strengthen the association between low ABI and incident CV events, we performed a sensitivity analysis after excluding patients with ABI≥1.40. All of the Cox proportional hazards analyses have been repeated after exclusion of such patients. This supplementary analysis showed no influence of patients with ABI≥1.40, leading to similar findings to those reported in the main analysis (►Table 3).

**Table 3: Baseline clinical and demographic characteristics according to vascular events occurrence.**

| | HR | 95% CI | P-value |
|---|---|---|---|
| Vascular Events | | | |
| Age (per year) | 1.060 | 1.041–1.079 | 0.001 |
| Any antithrombotic therapy | 0.476 | 0.343–0.661 | <0.001 |
| Low ABI | 1.503 | 1.111–2.032 | 0.008 |
| Vascular Death | | | |
| Age (per year) | 1.071 | 1.037–1.106 | <0.001 |
| Heart Failure | 2.229 | 1.312–3.788 | 0.003 |
| Any antithrombotic therapy | 0.389 | 0.221–0.684 | 0.001 |
| Low ABI | 2.237 | 1.342–3.732 | 0.002 |
| Myocardial Infarction | | | |
| Previous Myocardial Infarction | 2.199 | 1.070–4.522 | 0.032 |
| Low ABI | 2.618 | 1.319–5.197 | 0.006 |
| Myocardial Infarction* | | | |
| Low ABI | 2.568 | 1.110–5.940 | 0.027 |

CI= confidence interval; HR= hazard ratio. *in patients without previous myocardial infarction.

## Discussion

The principal finding of this study is that low ABI independently predicts MI and vascular death in NVAF patients. Our finding may facilitate cardiovascular risk assessment and stratification in NVAF patients.

NVAF is complicated by a high rate of vascular events despite antithrombotic treatment; this is outlined also by our population, which experienced a high rate of vascular events (3.81 per 100 patient-years). These findings are consistent with the results of recent clinical trials that compared warfarin with non-vitamin K antagonist oral anticoagulants. For example, in the ROCKET AF trial, including 7,133 patients assigned to warfarin therapy, 4.62 per 100 patient-years experienced stroke, vascular death and MI during a two-year median follow-up (24). Also, in the ARISTOTLE trial, including 9,081 patients assigned to warfarin therapy, a composite outcome of vascular events plus death from any cause was detected in 5.49 per 100 patient-years (25). In the ENGAGE AF-TIMI 38 trial, including 7,036 patients assigned to warfarin therapy, was reported a rate of 5.5 per 100 patient-years for major vascular events (MI, stroke, vascular death including bleeding) (26).

Even if ischaemic stroke of thromboembolic origin is considered the most important vascular event in AF population (27), it appears increasingly evident that the clinical history of AF may be complicated by vascular events of atherothrombotic origin such as MI (3, 4). In AF, systemic atherosclerosis is documented by plaque in the aortic arch (7), increased intima-media thickness (28) and low ABI (15), but it still remains unclear the impact of atherosclerosis per se on the vascular outcomes in patients with AF. In the present study, we focused our attention on the possibility of using ABI as a tool to detect higher risk of cardiovascular events occurrence in AF population. Low ABI indicates the presence of flow-limiting atherosclerosis in a peripheral artery and likely reflects the presence of generalised atherosclerosis (16). Low ABI has also been suggested as a tool for global cardiovascular risk assessment; indeed, a strong and consistent relationship between low ABI and cardiovascular events has been demonstrated in several clinical settings (10). In particular, results from MESA Study in 6,647 subjects free from cardiovascular disease, tested for ABI and followed-up for a mean observation of 5.3 years, showed that low ABI (defined as ABI< 1.0) was strongly associated with incident cardiovascular events (29). In particular, low ABI appeared to be able to predict coronary events (HR: 1.87, p=0.001). Conversely similar results could not be reported for stroke, since low ABI showed a weaker association with its occurrence (HR: 1.56, p=0.10) (29).

So far the impact of ABI on stroke, MI and vascular death in patients with AF has never been adequately explored. The ROCKET AF study showed similar rates of stroke between anticoagulated AF patients with and without symptomatic PAD (2.03 vs 1.95 events/100 patient-years) and a higher incidence of MI (2.02 vs 0.92 events per 100 patient-years), but the difference was not significant in this selected clinical trial cohort (30).

The results obtained from ARAPACIS study confirm a closer association between low ABI and vascular events, with a different impact on the typology of ischaemic events, also in AF setting. In particular, AF patients with low ABI were at higher risk of MI and vascular death, while no association was detected with stroke occurrence. In fact, in patients with AF stroke is prevalently of thromboembolic origin, rather than of atherosclerotic origin. The association between low ABI and MI is of interest taking into account the increasing evidence of the high rate of MI in AF patients, despite adequate anticoagulation and the lack of specific predictors. For example, the relationship between AF and MI has been recently investigated in a cohort of approximately 1,600 AF patients in whom the age-adjusted incidence rate of MI was 1.2 per 100 patient-years (31) during a median follow-up of 4.5 years. Consistent with this, our observed incidence rate for a new episode of MI was equal to 1.2 per 100 patient-years. Also, we confirm previous data from Roldan et al., which found even an higher event rate of MI compared to stroke in 978 AF patients on treatment with OAC and followed-up for two years (1.83%/year vs 1.66%/year, respectively) (32).

The association between low ABI and MI may be of relevance taking into account the serious issues related to the management of AF patients with MI, which could require the use of both anticoagulant and antiplatelet drugs, which would then be associated with a higher risk of bleeding. Preventing MI in AF patients would



 

therefore represent an important objective to improve AF management, but thus far, the risk factors helping to identify AF patients at risk of MI are elusive. Of particular interest, our study also shows the association between low ABI and MI in AF patients without a clinical history of MI, which underlines the potential usefulness of ABI measurement to identify AF patients at high risk of MI.

Finally, our data would seem to strengthen the emerging concept of a stronger pathophysiological link between AF and MI, involving more deep and complex relationships than the simple coexistence of similar risk factors (33, 34).

## Limitations

The population included in the study was derived from internal medicine sections participating in a voluntary registry and might not be fully representative of NVAF patients in Italy. Moreover, the study has been performed in a Caucasian population and therefore, these findings cannot be extrapolated to other ethnic groups. In accordance with previous data (35, 36), the ARAPACIS study shows a relatively large underuse of antithrombotic therapy in NVAF patients and of statins in patients with low ABI (37) and potentially at high risk of athero-thrombosis.

## Conclusions

In conclusion, AF patients with low ABI are at high risk of MI and vascular death and could be considered as a sub-set of 'high risk' patients, beyond stroke risk. These findings may represent a background for interventional trials aimed at evaluating the potential usefulness of anti-atherosclerotic drugs in reducing the risk of MI in AF patients with low ABI.

### Conflicts of interest

Gregory Y. H. Lip has served in Steering Committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. He is an investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. William R. Hyatt Grant awards in the past 2 years to CPC Clinical Research (a nonprofit academic research organization and affiliated to the University of Colorado) from the following sponsors: Aastrom, AstraZeneca, Bayer, National Institutes of Health, CSI, Cytokinetics, DNAVEC, Kowa, Kyushu University, Merck, Pluristem, Regeneron, Rigel, and Takeda. None of the other authors declares any conflicts of interest.

### What is known about this topic?

- Ankle-Brachial Index (ABI) is a reliable, non-invasive, inexpensive and simple instrumental evaluation of systemic subclinical atherosclerosis.
- Low ABI has been associated with an increased risk of vascular events in general population.
- Even if atrial fibrillation (AF) is prevalently associated with thromboembolic risk, there is evidence to indicate that AF carries also a high cardiovascular risk.

### What does this paper add?

- This study show, for the first time, that low ABI identifies non-valvular AF patients with high risk to develop cardiovascular events, in particular myocardial infarction and vascular death.

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