**Peripheral arterial disease in patients with atrial fibrillation:**

**The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study.**

**Running head:** arterial disease and atrial fibrillation

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# **Abstract**

*Background* Peripheral arterial disease has been linked with worse outcomes in patients with atrial fibrillation. The aim of this study is to assess the impact of peripheral arterial disease on mortality and stroke in a cohort of atrial fibrillation patients.

*Methods:* This was an ancillary analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial. A comparison of baseline characteristics was made between atrial fibrillation patients with and without diagnosed peripheral arterial disease. Multivariate cox regression analysis was performed to compare the risk of stroke, death and cardiovascular death among the two groups.

*Results:* The prevalence of peripheral arterial disease in the whole cohort of 4060 atrial fibrillation patients was 6.7%. Patients with peripheral arterial disease tended to be older, had higher prevalence of diabetes mellitus, hypertension and smoking, they were more likely to give a history of coronary artery disease, heart failure, cardiac surgery or cardiac intervention and stroke or TIA (all p<0.05). After multivariate adjustment, peripheral arterial disease was significantly associated with overall higher mortality (HR: 1.34, 95%CI 1.06- 1.70, p= 0.016) in atrial fibrillation patients, but the rates of ischaemic stroke were similar in the two groups (3.9% vs 3.5%, p= 0.874).

Subgroup analysis confined to the non-anticoagulated atrial fibrillation patients showed that peripheral arterial disease was an independent predictor of ischaemic stroke (HR: 3.37, 95%CI 1.25- 9.09, p< 0.016).

*Conclusion:* Peripheral arterial disease predicts higher mortality in atrial fibrillation, and was an independent predictor of ischaemic stroke in non-anticoagulated atrial fibrillation patients. Proactive surveillance and optimization of medical management in this group of patients is warranted, given the high risks associated with peripheral arterial disease where atrial fibrillation is also present.

*Key words:* Peripheral arterial disease, atrial fibrillation

# Introduction

Atrial fibrillation and peripheral arterial disease are two conditions associated with high risk of cardiovascular and cerebrovascular complications and mortality.1–5 There is evidence that coexistence of both these clinical conditions can result to an additive risk of adverse events.6 Indeed, atherosclerotic vascular disease has been linked with stroke, thromboembolism and death in subjects with atrial fibrillation and has been therefore included as one of the components of risk scores, such as the CHA2DS2-VASc score (Congestive Heart failure, Hypertension Age> 75 years, DM, Stroke, Vascular disease) in order to stratify risk in atrial fibrillation patients.7

The aim of this study is to assess the impact of peripheral arterial disease on mortality and stroke in a cohort of atrial fibrillation patients, as an ancillary analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial.

# Methods

The design and the primary results of the AFFIRM study have been reported.8,9 Briefly, the AFFIRM was a randomized, multicenter comparison of treatment strategies (rate control strategy or rhythm control strategy) in patients with atrial fibrillation who were at least 65 years of age or who had other risk factors for either stroke or death. Each participating site’s Institutional Review Board approved the study protocol, and each patient signed informed consent.

Patients were categorized according to a positive or negative history of peripheral arterial disease, which was investigator defined. A history of significant cardiovascular diagnoses, associated risk factors and medication was recorded at the time of randomization, with an interview administered questionnaire. After randomization patients were assigned to regular follow up and clinical events including death, cardiovascular death and ischaemic stroke were recorded.

*Statistical analysis*

Descriptive statistics were used to compare baseline characteristics and clinical events in the two groups. Chi-square test was used to identify significant differences in nominal variables. Continuous variables were assessed for normality and Mann–Whitney U test was performed to compare medians of non-normally distributed variables.

For each of the examined outcomes (death, cardiovascular death, stroke) univariate and multivariate cox regression analysis was performed to estimate hazard ratios at presence of peripheral arterial disease and other clinically relevant variables. Potential confounders that were inserted in multivariate regression were: age, gender, main cardiovascular risk factors (smoking, diabetes, hypertension), medical history (myocardial infraction, previous stroke or transient ischaemic attack, heart failure) and medical treatment (warfarin, aspirin, lipid lowering medication). A forward conditional process was used, in order to select variables to be included in the final model. Statistical analysis was performed with IBM SPSS Statistics, Version 23. Significant differences were defined by p values lower than 0.05.

The same analysis was performed for the subgroup of atrial fibrillation patients not receiving oral anticoagulation in order to assess the impact of peripheral arterial disease on outcomes (particularly ischaemic stroke).

# Results

The AFFIRM Study enrolled 4060 patients at 213 sites in North America. A diagnosis of peripheral arterial disease was reported in 282 (6.7%) patients. Patients with peripheral arterial disease tended to be older, had higher prevalence of diabetes, hypertension and smoking, they were more likely to give a history of coronary artery disease, heart failure, cardiac surgery or cardiac intervention and stroke or TIA (all p<0.05). There was no significant difference in the ratio of patients on oral anticoagulation in the two groups (85.1% vs 84.5%, p=0.864)

Mean follow up was 3.5 years (range, 2-6 years). Patients with and without peripheral arterial disease were evenly assigned in the two arms of the study. In total, 666 (16.4%) patients died, including 331 (8.2%) cardiovascular deaths and 157 (3.9%) ischaemic stroke events during follow up.

Baseline characteristics of the two groups and clinical outcomes are summarized in Table 1. During the follow up period peripheral arterial disease patients had higher mortality (29.4% vs 15.4%, p<0.001) and cardiovascular mortality (16% vs 7.6%, p<0.001), but there was no significant difference in the rates of ischaemic stroke (3.9% vs 3.5%, p=0.77).

On univariate Cox regression analysis, peripheral arterial disease predicted all-cause mortality (hazard ratio (HR): 2.07, 95% confidence interval (CI) 1.65- 2.61, p< 0.001), cardiovascular mortality (HR: 2.27, 95% CI 1.66- 3.11, p<0.001) and the combined outcome of stroke or death (HR: 1.87, 95% CI 1.50- 2.33, p< 0.001) but there was no significant correlation between peripheral arterial disease and risk of ischaemic stroke. On multivariate analysis, peripheral arterial disease remained an independent predictor for overall mortality (HR: 1.34, 95%CI 1.06- 1.70, p= 0.016) (Figure 1) and the combined outcome of stroke or death (HR: 1.28, 95%CI 1.02- 1.61, p= 0.037) but not for cardiovascular mortality (p=0.178) or stroke (p=0.674), (Table 2).

*Sensitivity analyses*

The subgroup not receiving oral anticoagulation consisted from 626 patients. Rates of death, cardiovascular death and stroke in this group were 21.4%, 9.3% and 4.6% respectively. On univariate analysis, peripheral arterial disease was associated with death (HR: 2.40, 95%CI 1.44- 4.00, p= 0.001), cardiovascular death (HR: 2.98, 95%CI 1.46- 6.06, p= 0.003), ischaemic stroke (HR: 3.42, 95%CI 1.30- 8.97, p= 0.012) and the combined outcome stroke or death (HR: 2.49, 95%CI 1.54- 4.04, p< 0.001). On multivariate cox regression model, peripheral arterial disease was an independent predictor of ischaemic stroke (HR: 3.37, 95%CI 1.25- 9.09, p< 0.016), (Table 3).

# Discussion

The principal finding of this study is the association of peripheral arterial disease with worse survival in atrial fibrillation patients. Second, peripheral arterial disease was an independent predictor of ischaemic stroke amongst non-anticoagulated atrial fibrillation patients which is perhaps the more appropriate subgroup of interest, since we are asking the question if peripheral arterial disease is a stroke risk factor per se (hence, requiring anticoagulation), and the event rates presented are not influenced by anticoagulation.

In general population studies, peripheral arterial disease is considered an indicator of generalised atherosclerosis and is associated with increased risk of overall mortality, cardiovascular mortality, major coronary events and stroke.1,2 This study adds to existing evidence, showing that peripheral arterial disease is a predictor of mortality in patients with atrial fibrillation. Unsurprisingly, peripheral arterial disease patients in this cohort had a more unfavourable risk profile, nevertheless this could not completely explain the higher mortality in this group.

Indeed, the present study reaffirms similar findings on mortality from other cohorts. In a Danish prospective cohort study of 3325 patients with atrial fibrillation, the adjusted hazard ratios (HR) for stroke, death and combined endpoint of stroke or death at presence of peripheral arterial disease were 0.87, 1.76 and 1.37 respectively.10 Similarly in the prospective APARACIS Study, in a cohort of 2,027 patients with atrial fibrillation, abnormal ankle-brachial pressure index (ABPI) predicted vascular death (HR= 2.05) and myocardial infraction (HR= 2.71), with 65.2% of the patients being on oral anticoagulation. 11 On the other hand, a sub-study on 2975 patients from the EORP-AF cohort, with 59.9% of patients receiving oral anticoagulation, did not demonstrate independent relation between peripheral arterial disease and mortality or CV mortality.12 Second, peripheral arterial disease did not cause significant increase in stroke rate in this study, when the whole cohort was examined, with 85% of the patients being on warfarin. This is consistent with the findings from previous studies10,11.

However, in non-anticoagulated patients, we found that peripheral arterial disease is a strong and independent predictor of stroke. This justifies its inclusion into stroke risk stratification scheme, such as the CHA2DS2VASc score, scoring 1 point for a V criterion13 14. Similarly, in a Taiwanese cohort of 7920 non-anticoagulated patients with atrial fibrillation, peripheral arterial disease was independently associated with ischaemic stroke (Odds ratio = 1.81).15 Oral anticoagulation has been reported to reduce stroke by 64% and all-cause mortality by 26% in atrial fibrillation16, which possibly explains the attenuated correlation between peripheral arterial disease and stroke in patients that do not receive oral anticoagulant therapy.

**Limitations**

This study has several limitations. It is a retrospective study on a trial dataset that was designed for different enquiries. The definition of peripheral arterial disease is based on clinical history and previous diagnosis of the disease. It is known that in the majority of cases peripheral arterial disease is asymptomatic17,18, we can therefore expect that this condition was possibly under-recorded. Additionally, those cases who were recorded, were most likely the symptomatic ones, which could reflect more advanced peripheral arterial disease and higher burden of atherosclerosis in these patients. However, there are no available data on stage and severity of peripheral arterial disease. Cohort studies that used screening tests (ABPI measurements) to detect peripheral arterial disease, have reported prevalence of peripheral arterial disease in patients with atrial fibrillation from 21% to 27% 11,19 which is considerably higher than the rate of diagnosed peripheral arterial disease in this study (6.7%). Despite the difference in prevalence of peripheral arterial disease, the conclusions from these studies were similar, indicating worse survival in atrial fibrillation patients with peripheral arterial disease.

**Conclusion**

Peripheral arterial disease predicts higher mortality in atrial fibrillation, and was an independent predictor of ischaemic stroke in non-anticoagulated atrial fibrillation patients. Proactive surveillance and optimization of medical management in this group of patients is warranted, given the high risks associated with peripheral arterial disease where atrial fibrillation is also present.

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Table 1. Baseline characteristics of atrial fibrillation patients with and without peripheral arterial disease.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **No PAD**N= 3778 (93.3 %) | **PAD**N= 282 (6.7%) | **P** |
| **Demographics** |
| Median Age (IQR) | 71 (11) | 72 (10)  | 0.002 |
| Male % | 60.4 | 65.2 | 0.108 |
| Ethnic Minority % | 11.3 | 12.1 | 0.700 |
| **History prior to randomization %** |
| Hypertension  | 70.1 | 80.9 | <0.001 |
| Diabetes | 19.2 | 30.5 | <0.001 |
| Smoking | 11.4 | 23.8 | <0.001 |
| Coronary artery disease | 36.4 | 62.4 | <0.001 |
| Myocardial Infraction | 16.1 | 34.4 | <0.001 |
| Angina | 24.2 | 46.5 | <0.001 |
| Congestive Heart Failure | 21.7 | 41.8 | <0.001 |
| CABG | 11.2 | 30.1 | <0.001 |
| Cardiac Intervention | 8.3 | 14.5 | <0.001 |
| Pacemaker | 5.9 | 9.6 | 0.013 |
| Stoke/ TIA | 12.9 | 19.5 | 0.002 |
| Pulmonary Disease | 13.4 | 29.4 | <0.001 |

|  |
| --- |
| **Medication prior to randomisation %** |
| Aspirin  | 26.3 | 30.5 | 0.127 |
| Warfarin | 85.1 | 84.5 | 0.800 |
| Aspirin and Warfarin | 16.6 | 21.6 | 0.031 |
| Angiotensin/ ACE inhibitor | 38.2 | 48.6 | 0.001 |
| Beta blocker | 42.7 | 40.9 | 0.561 |
| Diuretic | 41.7 | 55.7 | <0.001 |
| Nitrate | 17.4 | 36.5 | <0.001 |
| Lipid lowering agent | 21.5 | 35.1 | <0.001 |
| **Study arm and follow up** |
| Median follow up days (IQR) | 1311(705) | 1225 (740) | 0.161 |
| Rate control arm  | 50 | 49.3 | 0.853 |
| **Events after randomisation %** |
| Stroke | 3.9 | 3.5 | 0.772 |
| Death | 15.4 | 29.4  | <0.001 |
| CV Death | 7.6 | 16.0 | <0.001 |
| Stroke or death | 18.1 | 31.2 | <0.001 |

PAD= Peripheral Arterial Disease, IQR= interquartile range, CABG= coronary artery bypass graft, TIA= transient ischaemic attack, ACE= angiotensin converting enzyme, CV= cardiovascular

Table 2. Multivariate Cox regression: factors predicting adverse clinical events and corresponding hazard ratios.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HR** | **95% CI** | **P** |
| **Death** |
| Age | 1.06 | 1.05- 1.08 | <0.001 |
| Female gender | 0.83 | 0.71- 0.98 | 0.028 |
| History of PAD | 1.34 | 1.06- 1.70 | 0.016 |
| History of MI | 1.49 | 1.25- 1.78 | <0.001 |
| History of Stroke or TIA | 1.58 | 1.30- 1.92 | <0.001 |
| History of CHF | 2.29 | 1.95- 2.69 | <0.001 |
| History of Diabetes | 1.51 | 1.27- 1.79 | <0.001 |
| History of Smoking | 1.60 | 1.29- 1.98 | <0.001 |
| Warfarin | 0.68 | 0.56- 0.83 | <0.001 |
| Lipid-lowering agents | 0.79 | 0.64- 0.96 | 0.020 |
| **Stroke or Death** |
| Age | 1.06 | 1.05- 1.07 | <0.001 |
| History of PAD | 1.28 | 1.02- 1.61 | 0.037 |
| History of MI | 1.55 | 1.32- 1.83 | <0.001 |
| History of Stroke or TIA | 1.55 | 1.29- 1.86 | <0.001 |
| History of CHF | 2.05 | 1.76- 2.39 | <0.001 |
| History of Diabetes | 1.48 | 1.26- 1.74 | <0.001 |
| History of Smoking | 1.55 | 1.27- 1.90 | <0.001 |
| Warfarin | 0.72 | 0.61- 0.87 | <0.001 |
| Lipid-lowering agents | 0.74 | 0.61- 0.89 | 0.001 |
| **Cardiovascular Death** |
| Age | 1.05 | 1.03- 1.07 | <0.001 |
| History of MI | 1.90 | 1.51- 2.40 | <0.001 |
| History of Stroke or TIA | 2.01 | 1.56- 2.60 | <0.001 |
| History of CHF | 3.17 | 2.53- 3.97 | <0.001 |
| History of Diabetes | 1.64 | 1.30- 2.08 | <0.001 |
| History of Smoking | 1.44 | 1.06- 1.97 | 0.021 |
| **Stroke** |
| Age | 1.03 | 1.01- 1.05 | 0.011 |
| Female gender | 1.59 | 1.15- 2.19 | 0.005 |
| History of MI | 1.93 | 1.33- 2.80 | <0.001 |
| History of Stroke or TIA | 1.59 | 1.07- 2.37 | 0.023 |
| History of Diabetes | 1.50 | 1.04- 2.15 | 0.030 |
| Lipid-lowering agents | 0.56 | 0.35- 0.88 | 0.011 |

HR= hazard ratio, CI= confidence interval, PAD= peripheral arterial disease, MI= myocardial infraction, TIA= transient ischaemic attack, CHF= congestive heart failure

Table 3. Multivariate Cox regression in non-anticoagulated subgroup: factors predicting stroke and corresponding hazard ratios.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HR** | **95% CI** | **P** |
| **Stroke** |
| History of PAD | 3.37 | 1.25- 9.09 | 0.016 |
| History of MI | 3.00 | 1.36- 6.61 | 0.006 |
| Lipid-lowering agents | 0.09 | 0.01- 0.70 | 0.021 |

HR= hazard ratio, CI= confidence interval, PAD= peripheral arterial disease, MI= myocardial infraction

Figure 1 Overall survival plot for patients with Atrial Fibrillation with and without Peripheral Arterial Disease (multivariate adjustment).

