**THE IMPACT OF ATRIAL FIBRILLATION ON OUTCOMES OF PERIPHERAL ARTERIAL DISEASE: ANALYSIS OF ROUTINELY COLLECTED PRIMARY CARE DATA**

**Running heard: Atrial Fibrillation and Peripheral Arterial Disease**

Antonios Vitalis MD, MRCSa,b,c, Krishnarajah Nirantharakumar MPH, MFPH, MRCP, MDa,

Rasiah Thayakaran BSc, MSc, PhDa, Rajiv K. Vohra MS PhD FRCSb, Mark Kay MD FRCSb,

Alena Shantsila PhDc\*, Gregory Y.H. Lip MD, FRCP, DFM, FACC, FESC, FEHRAc\*

[\*joint senior authors]

a Institute of Applied Health Research, University of Birmingham, Birmingham, UK

b Department of Vascular Surgery, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, UK

c Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK

Correspondence to: Dr Alena Shantsila, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool, UK, L7 8TX; [s.shantsila@liverpool.ac.uk](mailto:s.shantsila@liverpool.ac.uk);

tel +44 15179 58340

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## Abstract

**Background:** The combination of peripheral arterial disease and atrial fibrillation is linked with high risk of mortality and stroke. This study aims to investigate the impact of atrial fibrillation on patients with diagnosed peripheral arterial disease.

**Methods:** This is a retrospective study using The Health Improvement Network (THIN) database, which contains prospectively collected data from participating primary care practices. Patients with a new diagnosis of peripheral arterial disease between 01/08/1995 and 01/05/2017 were identified in the database alongside relevant demographic information, clinical history and medications. Every patient in the dataset with peripheral arterial disease and baseline atrial fibrillation (case), was matched to a patient without atrial fibrillation (control) with similar characteristics using propensity score matching. Cox-regression analysis was performed and hazard ratios (HR) calculated for the outcomes of death, stroke, ischaemic heart disease, heart failure and major amputation.

**Results:** Prevalence of atrial fibrillation in this cohort was 10.2%. All patients with peripheral arterial disease and atrial fibrillation (n=5685) were matched with 5685 patients without atrial fibrillation but otherwise similar characteristics. After multivariate analysis, atrial fibrillation was independently associated with mortality (HR: 1.18, 95% Confidence Interval (CI) 1.12- 1.26, p< 0.01), cerebrovascular events (HR: 1.35, 95%CI 1.17- 1.57, p< 0.01) and heart failure (HR: 1.87, 95%CI 1.62- 2.15, p< 0.01) but not with ischaemic heart disease or limb loss.

**Conclusion:** Inperipheral arterial disease patients, atrial fibrillation is a risk factor for mortality, stroke and heart failure. This emphasizes the need for proactive surveillance and holistic management of these patients.

**Keywords**: atrial fibrillation, peripheral arterial disease, stroke, anticoagulation.

## Introduction

Peripheral arterial disease is a major health problem associated with functional decline1 and more than double risk of overall mortality, cardiovascular mortality, major coronary events and cerebrovascular events.2,3 Proactive surveillance of peripheral arterial disease patients and recognition of potential risk factors for these adverse outcomes is of paramount importance. The prevalence of atrial fibrillation in peripheral arterial disease patients is high, ranging from 8% to 17.9% in different cohorts.4,5 There is an increasing evidence that coexistence of these conditions further increases the risk of mortality and stroke.6,7

The management of atrial fibrillation has progressed towards integrated or holistic care, based on the ABC (Atrial fibrillation Better Care) pathway, incorporating a. Anticoagulation/ Avoidance of stroke, b. Better symptom management and c. Cardiovascular and Comorbidity optimization.8,9 As part of the C criterion of the ABC pathway, attention to associated comorbidities is recommended. Given that peripheral arterial disease is common amongst atrial fibrillation patients7,10,11 and since atrial fibrillation patients are commonly managed in the primary care setting, additional insights into the clinical epidemiology and risks of atrial fibrillation amongst peripheral arterial disease patients in primary care are needed, to plan surveillance and management pathways.

In this study, we aimed to investigate the significance of atrial fibrillation as a risk factor in a cohort of peripheral arterial disease patients.

## Materials and Methods

This is a retrospective study of The Health Improvement Network (THIN) database. Data in the database are prospectively collected by participating primary care practices after every encounter with the registered patient. It includes clinical diagnosis and symptoms, laboratory results, drug prescriptions and data on smoking habits which are recorded using the hierarchical “Read Code” System.12 In addition, THIN data comprise demographic information, measurements of height and weight as well as information on social deprivation, which is expressed as quintiles of Townsend score13. It has been previously demonstrated that THIN data can be generalized to the whole UK population in regard to demographics, mortality rates and prevalence of major health conditions14.

The study protocol was approved by the Scientific Review Committee (ref: 17THIN061).

The database has been researched to identify all patients with a new diagnosis of peripheral arterial disease during the time period from 01/08/1995 to 01/05/2017. To ensure data quality, only practices registered with the database for more than a year were included. Baseline demographics, significant previous diagnosis (including atrial fibrillation), medication, smoking history, Townsend score, body mass index (BMI) and kidney function expressed by glomerular filtration rate (GFR) have been recorded.

Using propensity score matching, every patient in the dataset with peripheral arterial disease and baseline atrial fibrillation (case), was matched to a patient with peripheral arterial disease without atrial fibrillation (control) with the nearest possible characteristics in regard to age, sex, ethnicity, smoking, BMI, Townsend index, renal function, medical treatment, history of diabetes, hypertension, stroke or transient ischaemic attack, heart failure, ischaemic heart disease and year of entry in the study.

All cases were censored from the date of peripheral arterial disease diagnosis (index date) until the exit date which corresponds to one of the following: the date of death, the date of transfer to a different practice, the date when their practice stopped providing data or the end of the data collection the 17/01/2018. Cox-regression analysis was performed and hazard ratios (HR) with their 95% confidence intervals (CIs) were calculated for the outcomes of death, stroke, ischaemic heart disease, heart failure and major amputation (transtibial or higher). Only new diagnoses of stroke, ischaemic heart disease, heart failure and amputation that occurred during the follow up period were considered as incident outcomes; subjects with the investigated diagnoses at baseline were excluded from analysis. The variables included in the model were age, sex, ethnicity, smoking status, BMI, renal function, Townsend index, drug treatments (lipid lowering, antiplatelets and oral anticoagulants), background diagnosis of hypertension, diabetes mellitus and atrial fibrillation (Figure 1).

Statistically significant relations have been defined by p values lower than 0.05. Statistical analysis was performed using IBM SPSS Statistics, Version 23.

As shown before, anticoagulation treatment can mitigate the increased risk of adverse outcomes imposed by coexisting atrial fibrillation and peripheral arterial disease10. A subgroup analysis was therefore performed, including only the patients who were not receiving any anticoagulation, in order to assess the relation of atrial fibrillation and peripheral arterial disease in this group.

## Results

During the studied period of 22 years, 55,540 patients with new diagnosis of peripheral arterial disease were detected in the database with 5,685 (10.2%) having coexisting atrial fibrillation. After propensity score matching two equal groups were created: peripheral arterial disease and atrial fibrillation (N= 5685, cases) and peripheral arterial disease with no atrial fibrillation (N= 5685, controls). Baseline characteristics are summarized in Table 1.

On multivariate cox-regression analysis atrial fibrillation was significantly associated with mortality (HR: 1.18, 95%CI 1.12- 1.26, p< 0.01), incident cerebrovascular events (HR: 1.35, 95%CI 1.17- 1.57, p< 0.01) and heart failure (HR: 1.87, 95%CI 1.62- 2.15, p< 0.01), with no significant relation with ischaemic heart disease (HR: 0.97 95%CI 0.81- 1.78, p= 0.78) and limb loss (HR: 1.06, 95%CI 0.85- 1.32, p= 0.59) (Table 2).

*Subgroup analysis*

In total 5431 patients with peripheral arterial disease that were not receiving oral anticoagulation were included in this analysis. The prevalence of atrial fibrillation in this subgroup was 43.1% (N=2339). On multivariate cox-regression analysis, atrial fibrillation was significantly associated with mortality (HR: 1.34, 95%CI 1.24- 1.45, p< 0.01), incident cerebrovascular events (HR: 1.55, 95%CI 1.27- 1.88, p< 0.01) and heart failure (HR: 2.03, 95%CI 1.63- 2.53, p< 0.01), while there was no significant relation with ischaemic heart disease (HR: 0.98, 95%CI 0.74- 1.29, p= 0.87) and limb loss (HR: 1.23, 95%CI 0.86- 1.75, p= 0.25).

## Discussion

The principal finding of this study is that atrial fibrillation has a negative prognostic impact on patient with peripheral arterial disease and is related to higher mortality and higher risk of stroke and development of heart failure.

This is in accordance with previous reports, where in a recent metanalysis of 6 prospective studies on patients with symptomatic peripheral arterial disease, the average prevalence of atrial fibrillation was 11.4% and this was significantly associated with mortality (OR: 2.52) and major adverse cardiovascular events (OR: 2.54).15 When analysing the subgroup of patients not receiving oral anticoagulation these associations were strengthened.

There was no relation between baseline atrial fibrillation and rates of major amputation in this study. Previous evidence on the impact of atrial fibrillation on limb outcomes in peripheral arterial disease patients is limited. A study based on Taiwanese health insurance data reported 8-fold higher risk of amputation in patients with newly diagnosed peripheral arterial disease and atrial fibrillation compared to peripheral arterial disease patients without atrial fibrillation; however, the population characteristics in this study were different with very low reported prevalence of atrial fibrillation (0.4%).16

A single hospital study in England, has shown that peripheral arterial disease patients with atrial fibrillation are more prone to emergency peripheral arterial disease related admissions and in hospital mortality.4 Also, a sub-study of EUCLID trial on peripheral arterial disease patients has identified atrial fibrillation as one of the main risk factors for the development of acute lower limb ischaemia (HR: 1.8).17 In the REACH registry, the presence of the atrial fibrillation among patients with peripheral arterial disease at baseline doubled the risk of amputation at 2 years, but was not predictive of revascularization or deterioration of vascular claudication.18

Atrial fibrillation is a known predictor of mortality, stroke and heart failure in general population studies.19–23 atrial fibrillation and peripheral arterial disease share several common risk factors such as hypertension, DM and coronary artery disease.23 In our study we have shown that despite controlling for those risk factors the impact of atrial fibrillation on peripheral arterial disease patients remains significant. The exact mechanism that generates this association needs further investigation. Atrial fibrillation is the main cause of cardioembolic stroke and is related with three times higher risk of extracranial systemic thromboembolism.24,25 In addition, atrial fibrillation is associated with a prothrombotic or hypercoagulable state, with higher levels of circulating biomarkers of coagulation cascade and inflammation.25–27 Indeed, atrial fibrillation is an indicator of systemic atherosclerosis and potentially increased burden of atherosclerotic disease, for example, with increased carotid intima-media thickness on ultrasound.28,29

Several studies demonstrate the merit of screening for atrial fibrillation in high risk patients30,31 which has been reflected in recent guidelines.9 The findings of the study emphasize the need of comprehensive assessment of peripheral arterial disease patients for atrial fibrillation, given the high prevalence and associated risks. These patients need to be proactively treated according to the integrated care ABC (Atrial fibrillation Better Care) pathway and offered oral anticoagulation, better symptom management with rate or rhythm control and optimization of risk factors and co-morbidities.8,9

*Strengths and Limitations*

This study’s strength is its large sample of patients and long duration of follow up, but on the other hand there are several limitations. It is a retrospective study of administrative data which lack the accuracy of clinical data. Our data would not allow to make any distinction according to the burden/ clinical severity of peripheral arterial disease and clinical type of atrial fibrillation (permanent, paroxysmal persistent) and to investigate the impact of incident cases of atrial fibrillation.

## Conclusions

In conclusion, this study emphasizes the high risk of adverse outcomes in patients with peripheral arterial disease and coexisting atrial fibrillation. Proactive surveillance and optimal medical management of these patients is mandated.

## Acknowledgment

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Table 1*.* Baseline characteristics of patients with peripheral arterial disease and atrial fibrillation compared with peripheral arterial disease peripheral arterial disease patients without atrial fibrillation, after propensity score matching.

|  |  |  |
| --- | --- | --- |
|  | Peripheral arterial disease with no atrial fibrillation | Peripheral arterial disease with atrial fibrillation |
| N | 5685 | 5685 |
| Age Median (IQR) | 78.0 (14.2) | 78.3 (12.7) |
| Male (%) | 3322 (58.4%) | 3405 (59.9%) |
| BMI category | | |
| Obese (%) | 1297 (22.8%) | 1326 (23.3%) |
| Overweight (%) | 1972 (34.7%) | 1860 (32.7%) |
| Underweight (%) | 140 (2.5%) | 163 (2.9%) |
| Normal (%) | 1624 (28.6%) | 1776 (31.2%) |
| Missing (%) | 652 (11.5%) | 560 (9.9%) |
| Smoking status | | |
| Smoker (%) | 1066 (18.8%) | 940 (16.5%) |
| Discontinued (%) | 2243 (39.5%) | 2383 (41.9%) |
| Never smoker (%) | 2193 (38.6%) | 2220 (39.1%) |
| Missing (%) | 183 (3.2%) | 142 (2.5%) |
| Diabetes (%) | 1588 (27.9%) | 1659 (29.2%) |
| Hypertension (%) | 3429 (60.3%) | 3570 (62.8%) |
| eGFR< 30 (%) | 281 (4.9%) | 271 (4.8%) |
| Ischaemic Heart Disease (%) | 2403 (42.3%) | 2462 (43.3%) |
| Heart Failure (%) | 1532 (26.9%) | 1614 (28.4%) |
| Stroke-TIA (%) | 1330 (23.4%) | 1451 (25.5%) |
| Medication | | |
| Lipid-lowering (%) | 3364 (59.2%) | 3521 (61.9%) |
| Anticoagulant (%) | 2593 (45.6%) | 3346 (58.9%) |
| Antiplatelet (%) | 4408 (77.5%) | 4423 (77.8%) |

eGFR= estimated Glomerular Filtration Rate, BMI= Body Mass Index, TIA= Transient Ischaemic Attack

Table 2*.* Comparison of outcomes between patients with peripheral arterial disease and atrial fibrillation (cases) Vs peripheral arterial disease patients without atrial fibrillation (controls).

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Value | Death | | Stroke or TIA | | Ischaemic Heart Disease | | Heart Failure | | Amputation | |
|  | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls |
| Total number | 5685 | 5685 | 4234 | 4355 | 3223 | 3282 | 4071 | 4153 | 5605 | 5588 |
| Incidence N  (%) | 2617  (46.0%) | 2417  (42.5%) | 392  (9.3%) | 345  (7.9%) | 209  (6.5%) | 234  (7.2%) | 518  (12.7%) | 313  (7.5%) | 172  (3.1%) | 163  (2.9%) |
| Person years FU | 24,410 | 24,037 | 15,942 | 19,133 | 10,581 | 12,784 | 14,242 | 18,174 | 19,850 | 23,301 |
| Unadjusted HR (95% CI) atrial fibrillation vs no atrial fibrillation | 1.19 (1.13- 1.26) | | 1.30 (1.13- 1.50) | | 0.99 (0.82- 1.19) | | 1.93 (1.68- 2.22) | | 1.10 (0.89- 1.36) | |
| p value | <0.01 | | <0.01 | | 0.91 | | <0.01 | | 0.38 | |
| Adjusted HR (95% CI)  atrial fibrillation vs no atrial fibrillation | 1.18 (1.12- 1.26) | | 1.35 (1.17- 1.57) | | 0.97(0.81- 1.78) | | 1.87 (1.62- 2.15) | | 1.06 (0.85- 1.32) | |
| p Value | <0.01 | | <0.01 | | 0.78 | | <0.01 | | 0.59 | |

FU= Follow Up, HR= Hazard Ratio, CI= Confidence Interval, TIA= Transient Ischaemic Attack

Timeline

Description automatically generated

Figure 1**.** Visual representation of study timeline (comparison between exposed group [atrial fibrillation + peripheral arterial disease] and control group [peripheral arterial disease without atrial fibrillation], matched 1:1 by age, sex, ethnicity, smoking, body mass index, Townsend index, renal function, medical treatment, history of diabetes, hypertension, stroke or transient ischaemic attack, heart failure, ischaemic heart disease and year of entry in the study).

AF, atrial fibrillation; PAD, peripheral arterial disease.

**Highlights:**

* Atrial fibrillation in patients with peripheral arterial disease has a negative prognostic impact.
* Related to increased mortality (HR 1.18), risk of stroke (HR 1.35) and heart failure (HR 1.87).
* Patients with peripheral arterial disease and atrial fibrillation needed proactive surveillance and optimal management.