

## Prognostic Significance of Atrial Fibrillation in Lower Limb Amputee Patients

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### WHAT THIS PAPER ADDS

This analysis highlights that atrial fibrillation is prevalent in patients with lower limb amputation and associated with a twofold increased risk of adverse cardiovascular events during 2-year follow-up compared with patients without atrial fibrillation. These high risk patients often do not receive recommended oral anticoagulation therapy according to guidelines. Further studies are urgently needed to assess the efficacy and safety of novel oral anticoagulants in this high risk group of patients. Lower limb amputee patients with atrial fibrillation require special attention to reduce complications and improve outcome.

**Objective:** In patients with risk factors or established atherothrombosis, atrial fibrillation (AF) is associated with a poor prognosis compared with patients without AF. The aim of this study was to evaluate the prevalence of AF in patients with lower limb amputation (LLA) and its association with cardiovascular death and adverse cardiovascular events in long-term follow-up.

**Methods:** Observational prospective study of consecutive patients after index major (transfemoral and transtibial) LLA. The primary endpoint was cardiovascular death and secondary endpoint was a composite of adverse cardiovascular events at follow-up (acute myocardial infarction, contralateral lower limb amputation, and ischaemic stroke).

**Results:** Of 282 patients with LLA, 46 (16.3%) patients had AF. AF patients were significantly older compared with patients without AF (median 74.0, IQR 13.0 vs. median 67.0, IQR 14.8 years,  $p < .001$ ). Diabetes and smoking on the other hand were significantly less prevalent in patients with AF compared with those without AF (41.3% vs. 72.0%,  $p < .001$  and 56.5% vs. 76.3%,  $p = .01$ , respectively). 54.3% of patients with AF were on oral anticoagulation therapy. At a median follow-up of 24.0 months (IQR 19.0–32.0), 28.3% patients with AF died of cardiovascular causes versus 17.8% without AF (HRR 1.8, 95% CI 1.0–3.4,  $p = .06$ ). Adverse cardiovascular events occurred in 32.6% of patients with AF during follow-up versus 22.0% without AF (HRR 1.9, 95% CI 1.0–3.3,  $p = .03$ ). In multivariate Cox regression analysis, AF (HRR 2.3, 95% CI 1.3–4.2,  $p = .01$ ) and diabetes (HRR 2.1, 95% CI 1.1–3.9,  $p = .02$ ) were identified as independent predictors of adverse cardiovascular events during the follow-up.

**Conclusion:** AF is common in patients with LLA and associated with higher risk of adverse cardiovascular events during long-term follow-up.

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### INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population and is associated with increased rates of morbidity and mortality, poor quality of life, and reduced exercise capacity.<sup>1–3</sup> The prevalence of AF

in patients with risk factors for atherothrombosis or established atherothrombosis, such as peripheral artery disease, is substantially higher compared with the general population.<sup>4</sup> Patients with a history of both AF and established atherothrombosis or with multiple risk factors for atherothrombosis have an approximately twofold increase in the composite of cardiovascular death, myocardial infarction, or stroke compared with patients without AF.<sup>5</sup>

Lower limb amputation (LLA) is one of the most devastating complications of atherothrombosis and is increasingly important because of the growing incidence of peripheral artery disease and diabetes mellitus.<sup>6</sup> The annual incidence of LLA ranges from 3 per 100,000 in Spain and Japan to 44

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per 100,000 in American Indians.<sup>7,8</sup> Mortality rates for LLA are reported to be higher than mortality rates for some cancers.<sup>9</sup> Reported 30 day mortality after LLA ranges between 7% and 22%, 1 year mortality ranges between 10% and 52% and up to 77% at 5 years.<sup>10–15</sup>

Understanding factors that influence morbidity and mortality of patients with LLA contributes to their better treatment and may therefore prolong life, prevent or delay contralateral amputation, and reduce treatment costs.

Therefore, this study aimed firstly at estimating the prevalence of AF and secondly, at assessing the association of AF and long-term outcome in patients with LLA.

## MATERIALS AND METHODS

### Study design and population

This prospective observational study was conducted at a rehabilitation hospital which admits patients after LLA mainly from the City of Belgrade, which has a total population of approximately 1.7 million (16.4% aged 65 and over) according to data from 2011.<sup>16</sup> Consecutive patients admitted between January 1, 2013 and December 31, 2014, were included following index major (transtibial or transfemoral) LLA and a main diagnosis of peripheral artery disease, diabetes with vascular complications or infection, arterial embolism, and thrombosis. Patients who were not followed up for at least 1 year from admission were defined as lost to follow-up. Time to cardiovascular death or event, in months, was calculated from the date of the index amputation.

Data on cardiovascular risk factors, comorbidities, medications, previous cardiovascular events and intervention, and cause of amputation were obtained from two main sources: interview and clinical examination, and medical charts. Smoking is defined as having ever smoked. Valvular heart diseases included moderate and severe aortic stenosis, mitral stenosis, prosthetic heart valves, and mitral valve annuloplasty.

For the assessment of risk of stroke and bleeding in patients with AF, CHA<sub>2</sub>DS<sub>2</sub>-VASc score (one point each is assigned for congestive heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female sex, and two points are assigned for stroke/transient ischaemic attack or age ≥75 years) and HAS-BLED score (one point each is assigned for hypertension, abnormal renal function, stroke, bleeding history or predisposition, labile INR, age >65 years, drugs and alcohol consumption), respectively, were calculated according to the recommendations of the European Society of Cardiology.<sup>17</sup> Chronic heart failure was defined according to the European Society of Cardiology as left ventricular ejection fraction <50%.<sup>18</sup> Follow-up data were obtained by telephone interview between February 15 and 29, 2016. The study was approved by the institutional review board. The need for informed consent for this study was waived by the institutional review board.

### Clinical outcomes

The primary study outcome was cardiovascular death during the follow-up period. The secondary endpoint was a

composite of cardiovascular events during the follow-up period. Cardiovascular death was defined as death from myocardial infarction, contralateral critical limb ischemia, stroke, heart failure, abdominal aortic aneurysm rupture, and sudden death that was not otherwise specified. Adverse cardiovascular events of interest were acute myocardial infarction, contralateral lower limb amputation, and ischaemic stroke.

### Statistical analysis

Categorical variables are presented as absolute numbers (*n*) and percentages (%) and continuous variables as a median and interquartile range (IQR). Patients with AF were compared with patients without AF with respect to patient characteristics, cardiovascular risk factors, and comorbidities, medications and clinical outcomes using the chi-square test for categorical variables and Mann-Whitney *U* test for continuous variables. The Kaplan–Meier method with a log-rank test was used to compare distributions of long-term outcomes (cardiovascular death and adverse cardiovascular events) between the groups. The predictive value of baseline parameters (AF, age, female sex, diabetes, hypertension, hypercholesterolemia, smoking, coronary artery disease, chronic heart failure, chronic kidney disease, and valvular heart disease) concerning long-term outcomes was first tested by univariate Cox regression analysis. Results are displayed as hazard rate ratios (HRR) and 95% confidence intervals (95% CI). Variables with *p* < .10 in the univariate Cox regression analysis were included in the multivariate Cox regression analysis. All tests performed were two-sided, and *p*-values <0.05 were considered to be statistically significant. Follow-up completeness was assessed by follow-up index (FUI).<sup>19</sup> All analyses were performed with the IBM SPSS Statistics 20 (IBM Corp, Armonk, NY, USA). A post hoc power analysis was conducted using Power and Sample Size Calculation Software.<sup>20</sup>

## RESULTS

### Patient characteristics

Of 291 patients with LLA, nine patients were lost to follow-up and were excluded from all analyses (FUI  $0.97 \pm 0.13$ ). These nine patients did not differ significantly regarding age compared with the analyzed patients (*U* 1035.3, *p* = .35). One of these nine patients was female and two patients had AF. The median age of 282 analyzed patients (75.5% males) was 68.0 (IQR 14.0) years. The median time from amputation to admission to rehabilitation was 1 month (IQR 1–3 months). The baseline characteristics, cardiovascular risk factors, comorbidities, previous heart and lower extremity revascularization, and medication use are listed in Table 1. Most patients had transfemoral amputation (71.3%). Patients with AF were older and were significantly more likely to have chronic heart failure and valvular heart disease. Diabetes and smoking, on the other hand, were significantly less prevalent in patients with AF compared with those without AF. All lower limb amputee

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