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Atrial fibrillation is a risk marker for worse in-hospital and long-term outcome in patients with peripheral artery disease

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ABSTRACT

Objectives: To investigate the relevance of atrial fibrillation or flutter (AF) for outcome of patients who are hospitalized for peripheral artery disease (PAD) and/or critical limb ischemia (CLI).

Methods and results: We compared baseline data, co-morbidities, procedural data as well as in-hospital and long-term outcome of 41,882 patients who were hospitalized with PAD or CLI between 2009 and 2011 according to whether they did or did not have atrial fibrillation/flutter. Follow-up was available until December 2012. Of these, 5622 patients (13.4%) had AF. AF patients were significantly older (78 ± 9 vs. 70 ± 11 years) and had significantly more comorbidities, such as diabetes (40.8 vs. 31.1%), chronic kidney disease (40.1 vs. 19.0%), coronary artery disease (38.0 vs. 23.0%) and chronic heart failure (26.9 vs. 7.2%, each $p < 0.001$). They had more advanced PAD as shown by higher Rutherford classes. In-hospital complications including acute renal failure, myocardial infarction, stroke sepsis and death occurred significantly more often (each $p < 0.001$). Duration of hospital stay was significantly longer and costs were markedly higher in patients with AF (each $p < 0.001$). Using multivariate Cox regression analyses regarding long-term outcomes, AF was an independent predictor for death (HRR 1.46; 95% CI 1.39–1.52, $p < 0.001$), ischemic stroke (HRR 1.63; 95% CI 1.44–1.85) and amputation (HRR 1.14; 95% CI 1.07–1.21).

Conclusion: Presence of AF in patients admitted for PAD and CLI is associated with worse in-hospital and long-term outcome than in patients without AF. This effect was independent of numerous other comorbidities and stage of vascular disease.

1. Introduction

Atrial fibrillation (AF) and peripheral artery disease (PAD) share many risk factors and often coexist [1]. The prevalence of both diagnoses increases with age and the combination of both is not uncommon. In the REACH registry (REduction of Atherothrombosis for Continued Health), Goto et al. reported an AF prevalence of 11.5% in patients with PAD compared to 2.3% in the general population [2]. PAD, on the other hand, was present in 4% of AF patients in the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan For Prevention of Vascular Events) [3] and 3% in the ACTIVE A trial [4]. In the Euro Heart Survey, 7.6% of hospitalized AF patients had PAD [5] and in a Danish AF population 17.4% carried this diagnosis [6]. Registry data from the German Competence NETwork on Atrial Fibrillation revealed increasing AF prevalence depending on the type of AF: In patients with first detected or paroxysmal AF 5.2% and 5.3% had PAD, increasing to 6.7% in patients with persistent and 8.7% in patients with permanent AF [7].

Both, AF and PAD for themselves, are associated with markedly increased cardiovascular mortality. Presence of PAD in patients with AF has been shown to increase risk of worse outcome mainly due to increased stroke risk [1,2,8,9]. Vascular disease, defined as prior myocardial infarction, peripheral artery disease and aortic plaque, has therefore been included as risk factor for stroke [10] when the previous $CHADS_2$ score was developed further to the CHA_2DS_2-VASc score [11]. When comparing patients with and without PAD as the only risk factor, Brønnum Nielsen et al. [12] very recently published a hazard ratio for a thromboembolic event of 2.7 (95% confidence interval 1.7–4.2) or rather a stroke rate of 4.85 per 100 person-years. Their stratified analysis of 987 patients with PAD revealed that peripheral artery disease was associated with a higher event rate when compared with myocardial infarction as a risk factor. Of note, PAD seems to have an even higher impact on prognosis in some non-white ethnic groups with AF [13].

Whether AF has a similar impact on outcome of patients with PAD as PAD has on patients with AF is less well known. One study on 388 patients with PAD who were admitted to a Birmingham hospital between

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1998 and 2000 showed a 2.5-fold increased risk of in-hospital death if patients also had AF [8]. Recent registry data showed that patients with PAD had a high and similar incidence of stroke and myocardial infarction and the highest incidence of bleeding when compared to patients with coronary artery disease and cerebrovascular disease [14].

A growing group of PAD patients will be diagnosed with AF due to an aging population and high incidence of common risk factors. The socio-economic burden of this combination may be huge despite progress in prevention and treatment of either disease. We therefore aimed to investigate the impact of atrial fibrillation on outcome in a large consecutive cohort of patients who were initially admitted for PAD and/or critical limb ischemia (CLI).

2. Methods

Data were derived from the BARMER GEK database, which is Germany's largest public health insurance company insuring more than 8 million people (approximately 10% of the population). The diagnosis and procedure related reimbursement system (Diagnosis related groups, DRG) requires data transfer of baseline patient characteristics, diagnosis causing hospital admission, comorbidities, procedural data and complications from the hospital to the insurance company in order to receive reimbursement as described in detail previously [15,16]. This system ensures detailed coding of diagnoses and procedures as well as complications. All patient data are stored in a central computerized database, from which we obtained anonymized data of all patients who fulfilled the inclusion criteria [16].

2.1. Study population

Patients with an index hospitalization between January 1st 2009 and December 31st 2011 and a main diagnosis of lower limb PAD or a secondary diagnosis of lower limb PAD (ICD-10 codes I70.20 to I70.24) in combination with a main diagnosis of diabetes with vascular complications, other peripheral vessel disease, arterial embolism and thrombosis, or ulcers were included (Supplemental Table S1). The Rutherford classification defines PAD stages: Mild, moderate and severe claudication as Rutherford class 1 to 3 (I70.20 or I70.21), respectively, ischemic rest pain as class 4 (I70.22) and PAD with minor and major tissue loss as class 5 and 6 (I70.23 and I70.24), respectively. The respective Rutherford class was determined for each patient according to the coded main or secondary diagnosis. Patients with Rutherford classes 4 to 6 were classified to suffer from CLI [17,18]. Moreover, any comorbidities were detected from coded secondary diagnosis, e.g. an diagnosis of obesity (ICD-10 E66) was defined as body mass index ≥30 kg/m^2.

All in- and outpatient cardiovascular diagnoses (ICD-codes) and procedure (OPS-codes) codes during 24 months before their index hospitalization were obtained for all patients (Supplemental Table S1, 16). Types and anatomic locations of procedures during the index-hospitalization were classified according to the respective OPS code. In-hospital complications including death, amputation, infection, stroke and myocardial infarction were assessed based on specific secondary diagnoses. Patients were divided into two groups by whether or not they carried the diagnosis of atrial fibrillation or flutter (ICD-10 I48*).

2.2. Follow-up

For each patient, all in- and outpatient diagnoses and procedures after the index hospitalization were obtained until December 31st, 2012 which allowed a minimum follow-up of one year. All major adverse events including amputation, myocardial infarction, stroke and death were included in the analysis.

2.3. Cost

An independent institute calculates total actual costs in all DRGs for entire Germany. On this real life basis, DRG cost weights are calculated for each DRG which are then used for in-hospital care reimbursement the following year. Thus, the German reimbursement system is based on actual cost for a specific health care service [15]. The presented data on cost represent all in-hospital reimbursement including physician payments, medication, blood-products and procedure-related material. Outpatient-related cost is not included.

2.4. Statistical analysis

Categorical variables are presented as absolute numbers (n) and percentages (%) of each subgroup. Statistical comparisons were made using the chi-square test. Continuous variables are presented as mean ± standard deviation (SD) and were compared with the ANOVA-F-test. The predictive value of baseline parameters concerning long-term outcomes was tested by multivariate Cox regression analysis. Results are displayed as hazard rate ratios (HRR) and 95% confidence intervals (CI). A logistic regression model predicting the presence of AF was used to calculate a propensity score (PS). All important baseline characteristics and comorbidities (see Table 1) were included. A 1:1 PS matching was performed using two extensions developed for SPSS based on Python (FUZZY and PSM). The resulting matched dataset was checked with regard to its balancedness by performing statistical tests and calculating standardized differences. Cox regression and binary logistic regression models were then performed with the PS matched dataset to test if the presence of AF had an influence on long-term outcomes and in-hospital complications and treatment. All tests were performed two-sided, and p-values of <0.05 were considered statistically significant.

Table 1
Baseline characteristics and comorbidities.

	With AF	No AF	Total	p
Patients, n (% of all)	5622 (13.4)	36,260 (86.6)	41,882 (100.0)	
Age, mean ± SD	78.1 ± 8.9	70.4 ± 11.4	71.4 ± 11.4	<**0.001**
Women, n (%)	2671 (47.5)	15,920 (43.9)	18,591 (44.4)	<**0.001**
Rutherford 1–3	1609 (28.6)	19,588 (54.0)	21,197 (50.6)	<**0.001**
RF 4	832 (14.8)	4521 (12.5)	5353 (12.8)	
RF 5	1378 (24.5)	5538 (15.3)	6916 (16.5)	
RF 6	1803 (32.1)	6613 (18.2)	8416 (20.1)	
Hypertension, n (%)	4147 (73.8)	24,338 (67.1)	28,485 (68.0)	<**0.001**
Obesity, n (%)	369 (6.6)	2704 (7.5)	3073 (7.3)	**0.017**
Dyslipidemia, n (%)	1540 (27.4)	11,414 (31.5)	12,954 (30.9)	<**0.001**
Smoking, n (%)	210 (3.7)	4495 (12.4)	4705 (11.2)	<**0.001**
Diabetes, n (%)	2293 (40.8)	11,268 (31.1)	13,561 (32.4)	<**0.001**
CAD, n (%)	2137 (38.0)	8328 (23.0)	10,465 (25.0)	<**0.001**
Chronic heart failure, n (%)	1514 (26.9)	2609 (7.2)	4123 (9.8)	<**0.001**
CKD, n (%)	2257 (40.1)	6898 (19.0)	9155 (21.9)	<**0.001**
Malignancies, n (%)	141 (2.5)	633 (1.7)	774 (1.8)	<**0.001**

AF indicates atrial fibrillation/flutter; CAD, coronary artery disease; CKD, chronic kidney disease. Bold p-values refer to statistically significant ($p < 0.05$).

3. Results

3.1. Patient characteristics

Data of 41,822 patients were included in the analysis. Baseline characteristics and comorbidities are summarized in Table 1. 5448 patients carried the diagnosis code for atrial fibrillation and 174 patients for atrial flutter. Patients with atrial fibrillation/flutter (AF) (13.4%) were significantly older than patients without AF and were more frequently female. AF patients had significantly more comorbidities including hypertension, diabetes, coronary artery disease, congestive heart failure and chronic kidney disease. Obesity, dyslipidemia and smoking on the other hand, were significantly less prevalent in patients with AF compared to those without AF. Patients with AF were in higher Rutherford classes (i.e. classes 4–6) compared to patients without AF.

Table 2
Treatment, complications and outcomes during index hospitalization.

	With AF	No AF	Total	p
Patients, n (% of all)	5622 (13.4)	36,260 (86.6)	41,882 (100.0)	
Peripheral angiography, n (%)	2985 (53.1)	20,081 (55.4)	23,066 (55.1)	**0.001**
Endovascular, n (%)*	1903 (34.2)	16,373 (45.9)	18,276 (44.3)	<**0.001**
Surgery, n (%)*	1477 (26.6)	9061 (25.4)	10,538 (25.5)	0.06
TEA, n (%)*	584 (10.5)	4380 (12.3)	4964 (12.0)	<**0.001**
Bypass, n (%)*	653 (11.7)	4539 (12.7)	5192 (12.6)	**0.041**
Any peripheral revascularization, n (%)*	3124 (56.2)	23,970 (67.2)	27,094 (65.7)	<**0.001**
Acute renal failure, n (%)	176 (3.1)	335 (0.9)	511 (1.2)	<**0.001**
MI, n (%)	99 (1.8)	218 (0.6)	317 (0.8)	<**0.001**
Ischemic stroke, n (%)	42 (0.7)	104 (0.3)	146 (0.3)	<**0.001**
Infections, n (%)	1285 (22.9)	4464 (12.3)	5749 (13.7)	<**0.001**
Sepsis, n (%)	270 (4.8)	713 (2.0)	983 (2.3)	<**0.001**
Amputations, n (%)	944 (16.8)	3457 (9.5)	4401 (10.5)	<**0.001**
Deaths, n (%)	426 (7.6)	791 (2.2)	1217 (2.9)	<**0.001**
In-hospital stay, mean ± SD, days	16.3 ± 16.1	10.5 ± 13.4	11.2 ± 14.0	<**0.001**
Costs, mean ± SD, €	6747 ± 7793	4991 ± 5200	5227 ± 5650	<**0.001**

AF indicates atrial fibrillation/flutter; endovascular, endovascular revascularization; MI, myocardial infarction; TEA, thrombendatherectomy. Bold p-values refer to statistically significant ($p < 0.05$).

* Numbers of revascularization procedures are given excluding the 533 patients with mild claudication.