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ATRIAL FIBRILLATION IN NON-ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS – WORSE CLINICAL PRESENTATION AND ADVERSE LONG TERM PROGNOSIS.

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ABSTRACT

BACKGROUND. Atrial fibrillation (AF) complicates the clinical course and treatment of acute coronary syndrome (ACS). The aim of this retro-prospective, two-center, observational study was to evaluate the clinical characteristics and 3-years prognosis of patients with non-ST-elevation myocardial infarction (NSTEMI) and AF. **MATERIAL AND METHODS.** Patients hospitalized with a diagnosis of NSTEMI were included. Baseline demographic and clinical features, in-hospital procedures, and occurrence of cardiovascular events in patients with sinus rhythm (SR) and AF confirmed before admission were analyzed. **RESULTS.** A total of 273 patients with NSTEMI were enrolled between 2012 and 2015, of whom 102 had AF (37.3%, 60.8% men) and 171 had SR (64.3% men). Patients with AF and NSTEMI were significantly older: 76.6±8.4 vs. 65.9±11.1 years ($p<0.0001$). The permanent pattern of AF was observed in 54 patients (52.9%) and paroxysmal in 48 patients (47.1%). They more often had heart failure with higher NYHA class ($p<0.0001$), type 2 diabetes ($p=0.0001$), abnormal renal function ($p<0.0001$), and history of stroke ($p<0.0001$). The presence of AF was not correlated with the number of stenotic coronary vessels. Significantly more NSTEMI patients with AF had a pacemaker implanted before admission ($p<0.0001$). Duration of hospital stay of NSTEMI AF patients was longer: 9.8 vs.7.0 days and it was related to age, Rho=0.5,$p<0.0001$. During the 2-year and 3-year follow-ups, AF was significantly related to higher mortality, both cardiovascular disease and all-cause mortality ($p<0.0001$). Independent long-term all-cause mortality predictors were heart failure, liver insufficiency, and age. At the 3-years follow-up, there were no significant differences in all-cause and cardiovascular mortality between groups with permanent AF and paroxysmal AF ($p=0.696$). **CONCLUSIONS.** Patients with atrial fibrillation and NSTEMI were older and more likely to have comorbidities. During the 2-year and 3-year follow-ups, AF was related significantly to higher mortality, both cardiovascular and of all causes. The long-term prognosis of patients with AF is adversely affected by heart failure, liver insufficiency, and age.

KEY WORDS : atrial fibrillation, NTEMI, long-term prognosis

INTRODUCTION

Despite the development of methods for early diagnosis and prevention of thromboembolic complications, atrial fibrillation (AF) remains one of the major causes of stroke, heart failure, and cardiovascular morbidity. In 2010 AF concerned 20.9 million men and 12.6 million women worldwide and the burden caused by arrhythmia is supposed to increase significantly in the near future [1-3]. Until 2030 the number of patients with AF in Europe may reach 14-17 million, while the prevalence of new cases is estimated to be within the range of 120 000-215 000 per year [4]. Acute coronary syndrome (ACS) occurs in many patients with AF. In the ARIC study, arrhythmia was associated with an increased risk of MI [5]. On the other hand, AF is observed in 7-10% of ACS cases. The diagnosis and therapy of patients with non-ST-elevation myocardial infarction (NSTEMI), who form a population twice the size of that of ST-elevation myocardial infarction (STEMI), remains a challenge. Despite a better initial clinical course, the long-term outcomes are worse. The optimal time to intervention, the scope of initial diagnostics, and risk stratification are still the subject of ongoing trials [6-8].

The main aims of this study were the demographic and clinical characteristics of AF occurrence in NSTEMI patients, the assessment of the arrhythmia impact on the treatment process and 2-year and 3-year prognosis.

METHODS

This was a prospective Cohort-study. The study was performed in the Cardiology Department of Schleswig Hospital in Germany (Helios Kinikum Schleswig) and in the 2nd Department of Coronary Artery Disease, Institute of Cardiology, Warsaw, Poland, from January 31, 2015, to December 31, 2019. The patients with NSTEMI were enrolled between 2012 and 2015, of whom 102 had AF (37.3%, 60.8% men) and 171 had SR (64.3% men). Data regarding the demographic and clinical features of patients were obtained from patients hospitalized since 2012 January, 01. All patients included in the study were monitored by family doctors during the post-hospitalization follow-up visits. The first contact occurred after discharge from the hospital. Medical history of the patient's general health, readmissions, deaths, and causes of death were obtained through phone or personal contact with general practitioners.

We assessed cardiovascular and all-cause mortality as well as the need for hospitalization in the two- and three-year follow-ups. The study was fully anonymized. and was approved by the Ethics Committee.

The authors have declared that no competing interests exist.

STATISTICAL ANALYSIS

Continuous data were presented as means and standard deviation (SD) or medians with the interquartile range (25-75th percentile). Categorical variables were reported as counts and percentages. Comparisons between groups were made using the Pearson's chi^2 test or Fisher's exact test for categorical variables and independent t-test or Mann-Whitney U-test for continuous data, as appropriate. For the longitudinal analysis, Kaplan-Meier survival curves were generated, and the log-rank test was used to assess differences in survival. All hypotheses tested were two-tailed, and p-values <0.05, were considered to indicate statistical significance. Cumulative survival rates were assessed using Kaplan-Meier analysis and compared with the log-rank test. Independent long-term all-cause

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mortality predictors were identified using Cox proportional hazards regression analysis. All statistical analyses were performed using the Statistical Analysis Software, SAS ver. 9.4.

RESULTS

The analysis was performed in 273 patients with ACS NSTEMI, including 102 (37.3%) patients with AF and 171 patients with sinus rhythm (SR). In both groups, the majority of the population was men, with 62 (60.8%) and 110 (64.3%). All patients were diagnosed with non-valvular AF. The paroxysmal pattern of arrhythmia was observed in 48 (47.1%) patients and permanent in 54 (52.9%) patients. The mean duration of paroxysmal AF was 2.3±1.2 days and permanent AF - was 3.2±1.9 years. Patients with AF were older : 76.6±8.4 vs. 65.9±11.1 years, p<0.0001, and they more often presented heart failure symptoms (NYHA Class III): 49 (48%) vs. 44 (25.7%), p<0.0001. In the group with AF, the following comorbidities were observed more frequently: hypertension, 97 (95.1%) vs. 157 (91.8%), p=0,3021; type 2 diabetes, 42 (41.2%) vs. 34 (19.9%), p=00002; and abnormal renal function, p<0.0001. Patients with AF more often had a history of previous stroke (19 [18.6%] vs. 5 [2.9%], p<0.0001; Table 1).

Patients with AF were treated initially with beta-blockers and digoxin intravenously to control the heart rate. Pharmacological cardioversion with amiodarone (n=24, 23.5%) or electrical cardioversion was performed (n=22, 21.6%). One patient spontaneously returned to sinus rhythm, and one patient died before cardioversion. The rate control strategy was chosen for patients with permanent AF (n=54, 52.9%).

Coronary angiography and percutaneous coronary intervention (PCI) were performed less often in the AF group than in the SR group (89 [87.2%] vs. 169 [98.8%], p<0.0001 and 83 [81.4%] vs. 168 [98.2%], p=0.0076) (Table 2). The coexistence of AF did not correlate with the severity of coronary artery disease; multivessel disease was observed in 52 (56.5%) patients with AF and NSTEMI and in 88 (51.8%) patients with SR and NSTEMI. Significantly more patients in the AF group had cardiac pacemaker (31 [30.4%] vs. 12 [7.0%], p<0.0001), but there was no difference regarding the presence of ICD (5.9% [AF] vs. 3.5% [SR], ns. Thromboembolic complications during hospitalization, such as stroke or transient ischemic attack (TIA), occurred more commonly in the AF group (12.7% vs. 2.3%, p=0,0006), and acute heart failure (9.8% vs. 5.9%, p=0,230) and bleeding events (13.7% vs. 4.1%, p=0,0039), especially of gastrointestinal origin. The duration of hospital stay was longer in patients with AF, after taking into account the age (9.8 vs. 7.0 days, Rho=0.25, p<0.0001).

In the AF group the in-hospital mortality rate was approximately twice that in the control group (5.9% vs. 2.9%, p=0.3402), but this did not reach statistical significance (Table 3). In 84% of cases, patients after NSTEMI with AF were discharged with anticoagulation recommendations: 46 patients were recommended pfenoprocoumarone, 15 patients were prescribed rivaroxaban, and the remaining group received periodic low-molecular-weight (n = 12) and unfractionated (n = 11) heparin. 11.86% patients with sinus rhythm developed AF during the 3-year follow-up period. rev.1

During the 2-year and 3-year follow-up, AF was significantly related to higher mortality, both cardiovascular disease and all-cause mortality (Table 4, figures 1, 2). Patients with arrhythmia more often required recurrent admission to the hospital (figure 3). Independent long-term all-cause mortality predictors were heart failure, liver insufficiency, and age (Table 4). At the 3-years follow-up, there were no significant differences in all-cause and cardiovascular mortality between groups with permanent AF and paroxysmal AF: 26/54 (48.2%) vs. 18/48 (37.5%), p=0.278 and 20/54 (37.0%) vs. 16 /48 (33.3%), p=0.696.

DISCUSSION

Patients with NSTEMI and AF had worse clinical presentations than those with SR. This was due to more advanced age and common comorbidities, such as diabetes, hypertension, and chronic kidney disease. These observations are in accordance with GRACE Registry population features, but in our study, no sex difference in the prevalence of AF was evident [9]. Thromboembolic events occurred more often in patients with AF, which probably resulted, at least in part, from the presence of arrhythmia. Yaghi et al. AF increased the risk of ischemic stroke after ACS by 58% [10].

The rates of coronary angiography and PCI procedures were lower in the AF group than in the SR group (87.2% vs. 98.8% and 81.4% vs. 98.2%, respectively. Mohamed et al. showed similar results in a recently published study [11]. Al Khdair et al. also indicated AF as a factor associated with suboptimal therapy [12]. There are several possible explanations for the delay in invasive treatment. The evaluation of patients with AF and suspected ACS is challenging. First, an increased concentration of troponin (Tn) and symptoms could have been attributed to an increased heart rate. Nevertheless, in patients with acute chest pain and AF, the diagnostic accuracy of hsTnI is high and comparable to that of patients without AF, especially after taking into account the change in hsTnI concentration [13]. Worse clinical status and implications related to stent implantation, such as the need for triple anticoagulant therapy or the risk of bleeding, could have favored conservative strategies. Nevertheless, the delay in coronary angiography has a negative impact on prognosis because effective revascularization may reduce the incidence of AF and improve prognosis [14, 15]. Our study presents an association between AF and the occurrence of heart failure symptoms and a decrease in the ejection fraction. The percentage of symptomatic heart failure was high in both groups (84.5% vs. 46.8%, p <0.0001). Patients with AF more often complain of herat failure symptoms. Nearly half of the patients reported shortness of breath with little exercise (NYHA class III), and 15.7% of them had dyspnea at rest (NYHA class IV). Systolic dysfunction of the left ventricle with an ejection fraction of <40% was observed in 23% of patients with AF and NSTEMI. Li et al. also reported a higher incidence of AF in patients with symptoms of heart failure (Killip class III and IV). They also observed a relationship between AF presence and inferior wall ischemia, as well as the involvement of the left circumflex coronary artery [14]. In our study, the left main coronary artery (LMCA) was more frequently assigned as an infarct-related artery in patients with AF.

Chronic kidney disease (CKD) is an important risk factor for AF. Renal failure contributes to severe atherosclerotic processes leading to coronary artery disease (CAD) and, consequently, to the occurrence of ACS. In contrast, AF is perceived as a risk factor for contrast-induced nephropathy (CIN) in NSTEMI [16]. The average renal function parameters in the AF group were significantly worse.

Patients with AF and NSTEMI more often had implanted pacemakers. In most cases, it was dual-chamber stimulation, suggesting implantation prior to the progression of AF to the permanent stage. Several studies identified right ventricular pacing as a risk factor for heart failure and the occurrence of AF [9, 17, 18]. Direct impact of the electrode as well as continuous or temporary right atrial pacing may lead to right atrial remodeling, including myocardial fibrosis.

The present study showed a relationship between the occurrence of AF and the duration of hospitalization. Patients with AF and NSTEMI ACS usually required longer hospital treatment, respectively 9.8 vs. 7.0 days, which could have been associated with a worse general condition at admission, more comorbidities, need for cardioversion, possible delay in coronary angiography due to elevated renal parameters (risk of post-contrast nephropathy), but also more frequent complications, i.e. thromboembolic events, bleeding or exacerbation of heart failure.

In the AF NSTEMI group, the percentage of in-hospital deaths was approximately twice that in the control group (5.9% vs. 2.9%, p = 0.3402), but this did not reach statistical significance. Stroke or transient ischemic attack (TIA), bleeding, and the need for

pacemaker implantation are associated with AF. Mehta et al. reported an increased hospital mortality and morbidity in patients with ACS and AF in the GRACE Registry, although only new-onset AF was an independent predictor of adverse events [9]. Similar conclusions were reported by González-Pacheco et al. [19]. Giglioli et al. identified the minimum time of AF, which worsens survival to 6 h [20]. In contrast, Maagh et al. showed that patients with chronic AF had a higher in-hospital mortality than those with new-onset AF or without AF [21]. Moreover, some publications did not confirm the independent risk associated with new-onset AF during ACS [22]. In a study by Batra et al. AF predicts a poorer prognosis than sinus rhythm, regardless of the form of the arrhythmia [23]. During the two- and three-year-follow-up in our study, the mortality rate was significantly higher in the AF group, which was previously presented in most, but not all, studies [24]. Apart from the risk of death, AF increases the probability of stroke, moderate or severe bleeding, and the need for recurrent hospitalization [25].

Both patients diagnosed with NSTEMI infarcts and patients with AF represent heterogeneous groups of patients with advanced age and a high percentage of comorbidities. The GRACE scale used to assess the risk of in-hospital death in patients with NSTEMI does not include AF as a prognostic factor. The guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology 2020 do not distinguish between patients with AF and NSTEMI, with the exception of anticoagulant treatment [26]. On the other hand, the ESC recommendations on atrial fibrillation (2020) do not address ACS NSTEMI, but only ACS as a category of cardiovascular events in terms of anticoagulant therapy [27]. Considering the increasing number of patients diagnosed with ACS NSTEMI and their poor prognosis, further studies are needed, especially in patients with AF, in order to optimize treatment and improve prognosis.

Limitations of the study

According to the initial statistical evaluation and modelling, the sizes of the groups do not allow for their matching, the paired groups would be too small, and the statistical power of the tests was weak. Due to the limited volume of the article, the small number of groups, and the difficulty in predicting the effectiveness and duration of the cardioversion effect, analyses of the interaction between rate and rhythm control were not included.

CONCLUSIONS

Atrial fibrillation contributed more often to complications such as stroke, bleeding, and the need for cardiac pacing in NSTEMI patients. During the 2-year and 3-year follow-ups, AF was related significantly to higher mortality, both cardiovascular and of all causes. The long-term prognosis of patients with AF is adversely affected by heart failure, liver insufficiency, and age.

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