The Long-Term Risk of Stroke in Patients with Acute Myocardial Infarction Complicated with New-Onset Atrial Fibrillation

Address for correspondence:
Milika Asanin, MD, MSc
Stanoja Glavasa 6
11000 Belgrade
Serbia
masanin@Eunet.rs

Asanin R. Milika, MD, MSc; Vasiljevic M. Zorana, MD, PhD; Matic D. Mihailo, MD, PhD; Mrdovic B. Igor, MD, PhD; Perunicic P. Jovan, MD, PhD; Matic P. Danica, MD, PhD; Vujisic-Tesic D. Bosiljka, MD, PhD; Stankovic Dj. Sanja, MSc; Matic M. Dragan, MD, MSc; Ostojic C. Miodrag, MD, PhD

Emergency Center, Clinical Center of Serbia, University Institute of Cardiovascular Diseases, Belgrade, Serbia

ABSTRACT

Background: The long-term risk of stroke after acute myocardial infarction (AMI) complicated with new-onset atrial fibrillation (AF) remains unclear. The aim of this study was to determine the long-term risk of AF and stroke in patients with AMI complicated with new-onset AF.

Methods: Patients with AMI complicated with new-onset AF (n = 260) and those without new-onset AF (n = 292) were followed for a mean of 7 years. All patients had sinus rhythm at hospital discharge.

Results: During the follow-up, AMI patients with new-onset AF had more frequent AF than those without new-onset AF (10.4% vs 2.7%, respectively; $P < 0.0001$). New-onset AF during AMI was a significant predictor of subsequent AF occurrence (the time elapsing between 2 consecutive R waves [RR] = 3.15, $P = 0.004$); but AF recurrence in follow-up (RR = 5.08, $P = 0.001$) and non-anticoagulation at discharge (RR = 0.29, $P = 0.008$) were independent predictors of stroke (Cox regression analysis). A period of 3.5 hours of AF within the first 48 hours of AMI was the high sensitivity cut-off level for the prediction of low long-term risk of stroke obtained by receiver operating characteristic analysis. Among patients who did not receive anticoagulants at discharge, the patients with short AF did not experience stroke and AF recurrence during follow-up, while those in the other group developed it (10.8%, $P = 0.038$ and 13.5%, $P = 0.019$, respectively).

Conclusion: New-onset AF during AMI identifies the patients at long-term risk for stroke who may potentially benefit from anticoagulant therapy. Atrial fibrillation recurrence in follow-up was independently related to the development of stroke. However, for low-risk patients with AF (those with short AF occurring early in AMI) long-term anticoagulants might not be required.

Introduction

New-onset atrial fibrillation (AF) complicates approximately 10% of acute myocardial infarction (AMI).[1–4] The most important underlying mechanism producing the new-onset AF is hemodynamic disturbance imposed by AMI.[5] The occurrence of new-onset AF reflects a poor clinical profile suggesting higher risk in patients with AMI.[2–8] Mostly, new-onset AF in its paroxysmal form complicates AMI,[1,8] and it may be recurrent in the postinfarction period. However, little is known about subsequent AF prognosis in these patients. In addition, it is not clear whether the arrhythmia burden is important as a risk factor for stroke in patients with new-onset AF.

The aims of this study were to determine the long-term risk of AF and stroke in patients with AMI complicated with new-onset AF.

Methods

Population of the Study

This study was composed of 320 consecutive AMI patients with new-onset AF who were admitted during 1996 to 1998 and 330 AMI patients without new-onset AF who were consecutively admitted between April and August 1996. A detailed description of this population has been reported previously.[1] The present study focused on patients who survived AMI—260 patients with new-onset AF and 292 patients without new-onset AF. Acute myocardial infarction was diagnosed by clinical, echocardiogram (ECG), and enzymatic findings. The diagnosis of AF had to meet the following criteria: absence of P waves, atrial activity represented by fibrillatory waves, and irregular the time elapsing between 2 consecutive R waves (RR) intervals. The term new-onset AF was used for any newly diagnosed AF that occurred during AMI with reversion to sinus rhythm prior to hospital discharge. All patients had sinus rhythm on the ECG obtained at discharge. Our article reported echocardiographic findings performed within 9.6 ± 2.7 days of hospital admission on average. The left ventricular wall motion score index was calculated using the 11-segment model of the left ventricle.[1] The patients were followed for a mean of 7 years (range, 5.5–8.5 years) after having been discharged from the hospital. They were controlled 1 month

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after discharge, after an additional 2 months, and thereafter every 3 months until the study was completed. The follow-up data were obtained for 99% of patients. A standard 12-lead ECG recorded occurrence of AF during outpatient follow-up. The episodes that occurred beyond planned routine visits were also recorded. Paroxysmal AF was defined as intermittent AF that was previously terminated without specific therapy. When episodes are longer than 7 days, AF was designated as persistent. Permanent AF includes cases of long-standing AF lasting over 1 year. Ischemic stroke was defined as a neurological deficit of sudden onset that persisted for more than 24 hours and was confirmed by CT scanning of the brain.

Statistical Analysis

Statistical comparisons were performed using the χ^2 for categorical variables and a student t test for continuous variables. Cox regression analysis was used to predict long-term risk of AF and ischemic stroke incidence. Kaplan-Meier curves were used to illustrate the incidences of AF and stroke occurrence over time. Receiver operating characteristic (ROC) analysis was performed to identify the most valuable AF duration within the first 48 hours of AMI for prediction of low risk of stroke during long-term follow-up period. Correlation analysis using the Pearson's coefficient was performed to assess clinical and ECG characteristics having an effect on short AF duration. A value of $P < 0.05$ was considered statistically significant. The SPS version 13.0 statistical package was used in the analyses (SPSS, Inc., Chicago, IL).

Results

Baseline Characteristics

The characteristics of the study population are summarized in the Table 1. The AMI patients with new-onset AF were significantly older and had heart failure (HF) more frequently than those without new-onset AF. According to ECG data, the AMI patients with new-onset AF had larger left atria and more extensive left ventricular systolic dysfunction than those in the other group. At hospital discharge, the groups were similar with respect to the prescription of aspirin, while more oral anticoagulation therapy was prescribed in patients with new-onset AF.

Table 1. Baseline Characteristics of AMI Patients with (Group I) and Without (Group II) New-Onset AF

	Group I (n = 260)	Group II (n = 292)	*P* Value
Age (years)	66.9 ± 9.1	58.3 ± 11.6	< 0.0001
Male gender (%)	68.8	72.3	0.379
Hypertension (%)	68.5	59.2	0.025
Diabetes mellitus (%)	29.6	20.9	0.018
Anterior AMI (%)	53.5	44.9	0.044
Thrombolysis (%)	24.6	24.3	0.935
Creatine kinase (U/L)	1146.5 ± 773.8	998.7 ± 740.1	0.022
Congestive heart failure (%)	48.5	15.1	<.0001
Killip class (I/II/III) (%)	51.5/35/13.5	84.9/11/4.1	<.0001
LA (mm)	39.4 ± 4.3	37.6 ± 2.9	0.001
LVEF (%)	43.3 ± 8.86	47.7 ± 9.28	<.0001
LVWMSI	2.12 ± 0.38	1.95 ± 0.33	<.0001
β-Blockers (%)	37.7	56.2	<.0001
ACE inhibitors (%)	57.3	35.6	<.0001
Amiodarone (%)	7.7	3.4	0.02
Aspirin (%)	91.9	91.4	0.837
Oral anticoagulant (%)	51.9	34.2	<.0001

Abbreviations: ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; LA, mean left atrial diameter; LVEF, left ventricular ejection fraction; LVWMSI, left ventricular wall motion score index.

Occurrence of AF during the Follow-Up Period

During the follow-up period, AF occurred in 10.4% (27 of 260) of patients with new-onset AF and 2.7% (8 of 292) of patients without new-onset AF, $P < 0.0001$ (Figure 1). The occurrence of AF was not equally distributed during the follow-up period. The incidence of AF in the first year was 6.5% (17 of 260) in patients with new-onset AF, while in patients without new-onset AF it was not recorded in this period ($P < 0.0001$). A total of 41% of these AF recurrences occurred within 3 months of hospital discharge. Paroxysmal AF was mainly noted in the first year after hospital discharge in patients with new-onset AF (62.5%), while after the first year persistent/permanent AF predominated in both groups.

The incidence of HF in follow-up was 31.5% in patients with new-onset AF and 17.8% in patients without it ($P < 0.0001$). Cox regression analysis showed that the presence of new-onset AF during AMI (RR = 3.15; 95% confidence interval [CI]: 1.42–7.00, $P = 0.004$) and HF in follow-up (RR = 4.87; 95% CI: 2.44–9.75, $P < 0.0001$) were associated with the increased risk of subsequent AF occurrence.

Occurrence of Stroke During the Follow-Up Period

An ischemic stroke during follow-up was identified in 5.8% (15 of 260) of patients with new-onset AF and 4.5% (13 of 292) of patients without new-onset AF (odds ratio [OR]: 1.31, 95% CI: 0.61–2.81, $P = 0.481$). The annual incidence

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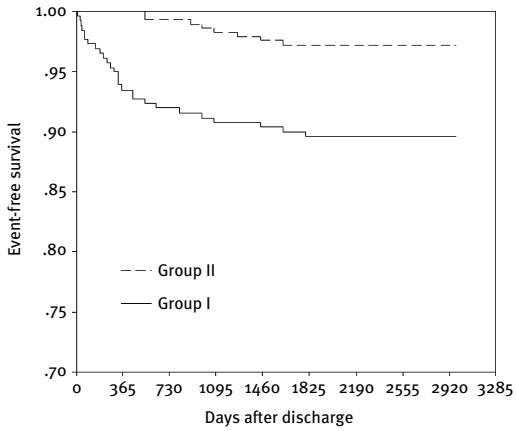

Figure 1. Kaplan-Meier curves of the rate of AF occurrence in AMI patients with (group I) and without (group II) new-onset AF (log-rank test, $P = 0.0002$). Abbreviation: AF, atrial fibrillation.

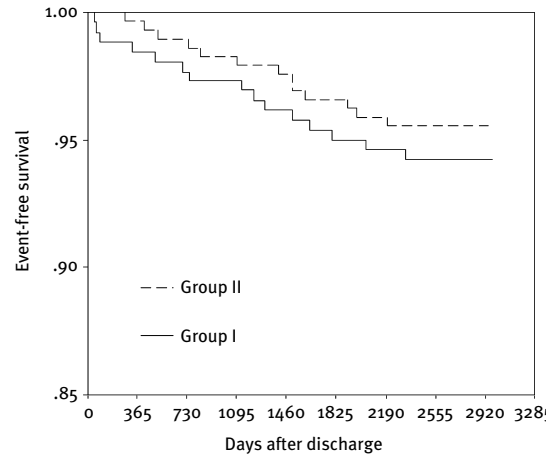

Figure 2. Kaplan-Meier curves of the rate of stroke occurrence in AMI patients with (group I) and without (group II) new-onset AF (log-rank test, $P = 0.473$). Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction.

of stroke was 1.5%, 0.8%, 0.4%, 1.1%, 1.1%, 0.4%, 0.4% per year in patients with new-onset AF and 0.3%, 0.7%, 0.7%, 0.7%, 1.0%, 0.7%, 0.3% per year in those without new-onset AF ($P = 0.882$). This represents a higher risk of stroke in patients with new-onset AF during the first year of follow-up. A large portion of the strokes (20%) in patients with new-onset AF occurred within 3 months of hospital discharge, thus, the risk of stroke was 1.1% in this period. The rates of stroke in the AMI patients with and without new-onset AF are illustrated in Figure 2. In patients with new-onset AF, stroke developed in 42.9% simultaneously with the recurrence of AF, but in the other group the development of stroke was not noticed simultaneously with occurrence of AF ($P < 0.01$). Cox regression analysis revealed that the independent risk factors of stroke were recurrence of AF (RR = 5.08, 95% CI: 1.92–13.42, $P = 0.001$) and HF in follow-up period (RR = 2.38, 95% CI: 1.06–5.32, $P = 0.034$). The patients who did not receive anticoagulation therapy at hospital discharge also had a significantly increased risk of ischemic stroke (RR = 0.29, 95% CI: 0.11–0.73, $P = 0.008$).

However, it is not clear how long episodes of new-onset AF during AMI have to last before anticoagulation is warranted. In particular, it is not known whether the short arrhythmia early in the course of AMI is an indication for long-term anticoagulants. A period of 3.5 hours of AF within the first 48 hours of AMI was the high sensitivity cut-off level for the prediction of low long-term risk of stroke obtained by ROC analysis with sensitivity and specificity of 100% and 68.5%, respectively (Figure 3). Out of the patients who did not receive anticoagulation therapy at discharge, the patients with AF < 3.5 hours (n = 37) did not experience stroke in the follow-up period, but those with AF $\geqslant$ 3.5 hours ($n = 74$) developed it 10.8% of the time ($P = 0.038$). In addition, the patients with short episodes of AF were without AF recurrences during follow-up, while

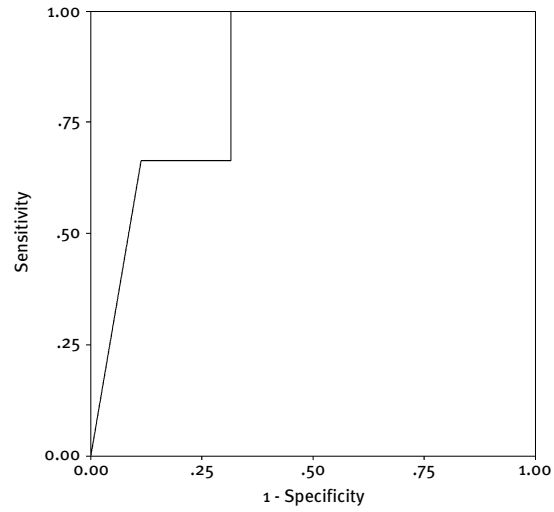

Figure 3. The ROC curve of AF duration within the first 48 hours of AMI in relation to long-term risk of stroke (area under the curve = 0.858, $P = 0.038$). Abbreviations: AF, atrial fibrillation; AMI, actue myocardial infarction; ROC, receiver operating characteristic.

patients in the other group suffered from AF recurrences 13.5% of the time ($P = 0.019$). The correlation analysis was performed to determine the factors that correlated with short AF duration. After correlation with age, gender, hypertension, diabetes, AMI location, thrombolysis, HF, left atrial size, left ventricular ejection fraction, left ventricular wall motion score index, a direct correlation was found between short AF duration and younger age ($P = 0.001$), more frequent inferior AMI ($P = 0.045$), thrombolysis ($P = 0.004$), less frequent HF ($P < 0.0001$), smaller left

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atrial size ($P < 0.0001$), higher left ventricular ejection fraction ($P < 0.0001$), and lower left ventricular wall motion score index ($P < 0.0001$).

Discussion

New-onset AF is a frequent complication of AMI. The course of new-onset AF in many AMI patients is characterized by paroxysmal form.[1,8] After hospital discharge, during a long-lasting period, these patients can relapse into AF. Data of AF recurrence after hospital discharge in patients with new-onset AF complicating AMI, however, are very scarce and limited to a select subgroup of patients. Siu et al[9] reported that AF developed in 34% (20 of 59) of patients with transient AF following the inferior AMI during a mean follow-up of 3.2 years. In this study, up to 10% of AMI patients with new-onset AF suffered from AF recurrence during a mean follow-up of 7 years. It is noteworthy that new-onset AF during the AMI and HF in follow-up increase the propensity for subsequent AF occurrence. As in this prior study,[9] we noted an abrupt increase in the proportion of patients with AF recurrence mainly in paroxysmal form soon after hospital discharge. It may suggest that the initiating factors of the AF onset during AMI are still present and the risk of recurrence early after discharge is high.

Another as yet unresolved issue is the long-term risk of stroke in patients with AMI complicated with new-onset AF. A previous study has reported that 1% of AMI survivors experienced stroke in the year after hospital discharge.[10] Siu et al[9] reported the annual incidence of ischemic stroke, during the first and second year of follow-up, at 10.2% and 7.5%, respectively, in patients with transient AF during inferior AMI when they were treated with antiplatelet therapy alone. In this study, the stroke incidence accounted for 1.5% in the first year after AMI with subsequent decline in the incidence of stroke. We found that the risk of stroke in patients with new-onset AF was highest within the 3-month period upon discharge, and we confirmed that development of stroke was independently related with recurrence of AF.[9] The AF recurrence possibly reflects the hemodynamic burden and severity of cardiovascular disease and may itself be the predisposition to stroke. The present study also confirmed that heart failure itself might contribute to a higher likelihood of stroke.[11,12] In the Cox analysis, new-onset AF during AMI was not a predictor of stroke in the follow-up period. However, oral anticoagulant therapy prescribed at hospital discharge was associated with reduced risk of stroke by 71% in the follow-up period ($P = 0.008$). More frequent use of anticoagulants in patients with new-onset AF may result in decreased incidence of stroke in these patients.

Our results demonstrate that new-onset AF during AMI identifies the patients at long-term risk for stroke. However, our analysis suggests that there may be differences with regard to potential risk of stroke and AF burden. It appears that a less aggressive antithrombotic approach may be employed in patients in whom new-onset AF occurred earlier during AMI and who had a short duration of arrhythmia. Maintenance of sinus rhythm was very good in these patients and without AF recurrence in follow-up period. This may be the consequence of the patients' younger age, better reperfusion, and better ECG parameters of left atrial size and left ventricular function.

The present study illustrates that oral anticoagulant therapy reduces the long-term risk of stroke in patients with new-onset AF during AMI. In addition, our results also provide evidence that patients with short AF duration, occurring early in AMI, were at low risk of stroke, in which long-term anticoagulation therapy might not be required. Additional studies are needed to confirm these statements in clinical practice.

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