ABSTRACT

Objective: In this study, we aimed to examine the prognostic impact of decreased kidney function at admission on the occurrence of new-onset atrial fibrillation (AF) in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI).

Methods: The study enrolled 3,115 consecutive patients with STEMI. Kidney function was assessed by estimation of the glomerular filtration rate (eGFR) at admission. Patients with cardiogenic shock at admission, patients on hemodialysis, and patients with a medical history of previous AF (paroxysmal, persistent, or permanent) were excluded. The follow-up period was six years.

Results: New-onset AF occurred in 215 (6.9%) patients, 75 (34.9%) patients presented with AF, and 140 (65.1%) patients developed AF after pPCI. The median time of AF occurrence in patients who did not present with AF was 4.5 (interquartile range 1–25) hours after pPCI. New-onset AF was associated with a higher short- and long-term mortality. In the multiple logistic regression analysis, all stages of reduced kidney function were independent predictors for the occurrence of new-onset AF, and negative prognostic impact increased with the deterioration of kidney function: eGFR <90 mL/min/m², hazard ratio (HR) 1.96, 95% confidence interval (CI) 1.42-2.89, p=0.011; eGFR 60-89 mL/min/m², HR 1.54, 95% CI 1.13-2.57, p=0.045; eGFR 45-59 mL/min/m², HR 2.09, 95% CI 1.24-3.38, p=0.023; eGFR 30-44 mL/min/m², HR 2.93, 95% CI 1.64-5.29, p<0.001; eGFR 15-29 mL/min/m², HR 5.51, 95% CI 2.67-11.39, p<0.001.

Conclusion: Decreased kidney function was significantly associated with the occurrence of new-onset AF, and its impact increased with the deterioration in kidney function, starting with an eGFR value of 90 mL/min/m². New-onset AF was an independent predictor of long-term all-cause mortality in the analyzed patients.

Keywords: new-onset atrial fibrillation, kidney function, myocardial infarction

Introduction

Atrial fibrillation (AF) frequently complicates acute ST-elevation myocardial infarction (STEMI) (1-3). New-onset AF complicating STEMI is defined as AF occurring during the index event. The incidence of new-onset AF in patients with STEMI is reduced by the introduction of primary percutaneous coronary intervention (pPCI) in comparison with the thrombolytic era, and it ranges from 4.8% to 7.7% (1, 4, 5). Multiple studies have shown that any type of AF that complicates STEMI is an independent predictor of mortality and adverse cardiovascular events in short-term and long-term follow-ups (1, 2, 5-10). However, there is a study showing that only before AF, but not new-onset AF, is an independent predictor of adverse events in patients with STEMI (11). Many factors and mechanisms may be related to new-onset AF development in patients with STEMI (2, 10). Some of these factors are excess catecholamine release or hemodynamic impairment, which is related to acute ischemia (2, 4, 10). Apart from factors directly linked to ischemia, chronic states, that is comorbidities can also influence frequent occurrence of new-onset AF in patients with STEMI. Most probably through the mechanism of structural atrial remodeling present in these
Kidney function was an independent predictor for the occurrence of new-onset atrial fibrillation (AF).

The independent predictive impact increased with the decline kidney function, starting with an estimation of the glomerular filtration rate (eGFR) value of 90 mL/min/m².

New-onset AF was an independent predictor of long-term all-cause mortality in the analyzed patients.

Study population, data collection, and definitions
This study enrolled 3,115 consecutive patients, hospitalized between February 2006 and December 2012, who were included in the prospective Clinical Center of Serbia STEMI Register. The goal of the prospective Clinical Center of Serbia STEMI Register has been published elsewhere (18). In brief, the objective of the register is to gather complete and representative data on the management and short- and long-term outcomes of patients with STEMI, undergoing primary PCI in the center. The study protocol was approved by the Local Research Ethics Committee. All the consecutive patients with STEMI aged 18 or older, who were admitted to the coronary care unit after undergoing pPCI in the center, were included in the register. Patients with cardiacogenic shock at admission, those on hemodialysis, and patients with a medical history of previous AF (paroxysmal, persistent, or permanent) were excluded from this study. Patients with no medical history of previous AF who had been treated with pPCI and to analyze the prognostic impact of new-onset AF on long-term all-cause mortality in these patients.

Methods

Statistical analysis
Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as median value (med) with 25th and 75th quartiles (IQR). Analysis for normality of data was performed using the Kolmogorov-Smirnov test. Baseline differences between groups were analyzed using the Mann-Whitney U test for continuous variables and the Pearson X² test for categorical variables. Multiple logistic regression was used to define independent predictors of new-onset AF (backward method, with p<0.10 for entrance into the model). The receiver operating characteristic (ROC) curve was used to test the predictive power of kidney function on new-onset AF development. The Kaplan-Meier method was used for constructing the probability curves for a six-year survival, and the difference between patients with and without new-onset AF was tested with the log-rank test. Multiple Cox analysis (backward method, with p<0.10 for entrance into the model) was used to identify independent risk factors for the occurrence of six-year all-cause mortality. A p value <0.05 was considered significant. The Statistical Package for the Social Sciences statistical software, version 19, was used for data analysis (SPSS Inc, Chicago, IL, US).
Results

New-onset AF occurred in 215 (6.9%) patients. Among the patients with AF, 75 (34.9%) presented with AF, and 140 (65.1%) developed AF after pPCI. The median time of AF occurrence in patients who did not present with AF was 4.5 (IQR 1-25) hours after pPCI. Median duration of new-onset AF was 18 (IQR 6.5-30) hours. Baseline demographic, clinical and laboratory data, angiographic characteristics, baseline kidney function, as well as ejection fraction (EF) in patients, who did and did not develop new-onset AF are shown in Table 1. In comparison with patients who did not have new-onset AF, patients with new-onset AF were older. The following were more frequently present in these patients—previous coronary disease, hypertension, cardiac insufficiency, lower systolic blood pressure and higher cardiac frequency at admission, three-vessel coronary disease, occlu-
sion of the infarct-related artery (pre-procedural flow TIMI=0) at the initial angiogram, postprocedural flow TIMI <3, and a lower value of EF. Patients with new-onset AF had a lower average value of eGFR on admission than patients without AF.

Data on therapy during hospitalization and at discharge is presented in Table 2. All the analyzed patients with new-onset AF were converted into sinus rhythm with medication (amiodarone), or they converted spontaneously on myocardial revascularization. The use of beta blockers, amiodarone, and digitalis was in accordance with the current guidelines and the existing practice in our coronary unit. No patients with AF were treated with direct current cardioversion.

Independent predictors for the occurrence of new-onset AF are presented in Table 3.

### Table 2. Therapy during hospitalization and at discharge from hospital

| Variable                  | New-onset AF | No AF | P-value |
|---------------------------|--------------|-------|---------|
| **In hospital**           | n=215        | n=2,900 |         |
| Aspirin, n (%)            | 215 (100)    | 2,899 (99.99) | 0.785   |
| Clopidogrel, n (%)        | 214 (99.99)  | 2,800 (96.55) | 0.872   |
| Heparin, n (%)            | 215 (100)    | 2,410 (83.11) | 0.009   |
| Beta blockers, n (%)      | 160 (74.41)  | 2,534 (87.37) | 0.504   |
| ACE inhibitors, n (%)     | 137 (63.72)  | 2,168 (74.75) | 0.001   |
| Statin, n (%)             | 173 (80.46)  | 2,138 (73.72) | 0.145   |
| Diuretics, n (%)          | 97 (45.12)   | 399 (13.75)   | <0.001  |
| Digitalis, n (%)          | 59 (27.45)   | 49 (1.68)     | <0.001  |
| Amiodarone, n (%)         | 59 (27.45)   | 26 (0.89)     | <0.001  |
| Inotropes                 | 54 (25.12)   | 138 (4.76)    | <0.001  |
| **At discharge**          | n=173*       | n=2,809*      |         |
| Aspirin, n (%)            | 171 (98.89)  | 2,539 (90.38) | 0.555   |
| Clopidogrel, n (%)        | 171 (98.89)  | 2,521 (90.25) | 0.952   |
| Beta blockers, n (%)      | 170 (98.26)  | 2,438 (86.79) | 0.224   |
| ACE inhibitors, n (%)     | 133 (76.87)  | 2,271 (80.84) | 0.764   |
| Statins, n (%)            | 143 (82.65)  | 2,539 (90.38) | 0.985   |
| Amiodarone, n (%)         | 72 (41.62)   | 95 (3.38)     | <0.001  |
| Digitalis, n (%)          | 5 (2.89)     | 10 (0.36)     | <0.001  |
| Diuretic, n (%)           | 49 (28.32)   | 429 (15.27)   | <0.001  |
| Oral anticoagulant therapy**, n (%) | 130 (75.12) | 5 (0.17) | <0.001 |

*Number of discharged patients; **Vitamin K antagonists

AF - atrial fibrillation

| Variable                  | OR  | CI     | P-value |
|---------------------------|-----|--------|---------|
| 66–75 years               | 1.80| 1.20–2.69 | 0.040   |
| >75 years                 | 2.40| 1.47–3.19 | <0.001  |
| Heart failure at admission| 2.64| 1.92–3.93 | <0.001  |
| Postprocedural TIMI <3    | 2.13| 1.33–3.42 | <0.001  |
| IRA occluded (TIMI=0)     | 1.67| 1.18–2.36 | 0.027   |
| eGFR <30 mL/min/m²        | 1.96| 1.42–2.89 | 0.011   |
| eGFR 30–44 mL/min/m²      | 2.93| 1.64–5.29 | <0.001  |
| eGFR 15–29 mL/min/m²      | 5.51| 2.67–11.39 | <0.001  |

AF - atrial fibrillation; OR - odds ratio; CI - confidence interval; TIMI - thrombolysis in myocardial infarction; IRA - infarct-related artery; EF - left ventricular ejection fraction; eGFR - estimated glomerular filtration rate
In the multiple logistic regression analysis, all stages of reduced kidney function were significantly associated with the occurrence of new-onset AF. The risk of occurrence of new-onset AF increased with the worsening kidney function. Figure 1 presents the discriminative ability of kidney function (eGFR) to predict the occurrence of new-onset AF (ROC curve).

In-hospital, 30-day, one-year, and six-year mortalities were significantly higher in patients with new-onset AF compared with that in patients with no AF: in-hospital mortality of 19.62% vs. 3.12%, respectively, \( p < 0.001 \); 30-day mortality of 20% vs. 3.58%, respectively, \( p < 0.001 \); one-year mortality of 23.26% vs. 5.58%, \( p < 0.001 \); and six-year mortality of 46.57% vs. 6.93%, respectively, \( p < 0.001 \).

Kaplan-Meier curves estimating the probability of mortality during follow-up in patients with new-onset AF and with no AF are shown in Figure 2. After adjustment for potential confounders, including age, heart failure at admission, EF, postprocedural TIMI flow <3, and kidney function; new-onset AF remained an independent predictor of mortality throughout the follow-up period–hazard ratio 1.85, (95% confidence interval 1.25-2.45), \( p = 0.024 \).

Discussion

The results of this study show that declining kidney function at admission was more frequently present in patients with new-onset AF compared with that in patients with no AF. Decreased kidney function at admission was significantly associated with the occurrence of new-onset AF. The impact increased with the decline in kidney function, starting with an eGFR value of 90 mL/min/m\(^2\). New-onset AF was an independent predictor of long-term all-cause mortality in the analyzed patients.

The incidence of new-onset AF in the patients from this study is consistent with data that can be found in literature related to patients treated with pPCI (1, 2, 5, 7, 20). The clinical characteristics of the patients with AF from this study mostly correlate with the results found in literature; the common finding is that patients with new-onset AF are older; more commonly have previous coronary disease as well as a greater number of chronic comorbidities and cardiac insufficiency and a poor coronographic finding are more commonly present at admission. Patients with new-onset AF generally have a lower EF after infarction (1, 2, 5, 8-10). However, although diabetes mellitus and hypertension are considered to be predictors of AF occurrence in our study, there was no significant difference in the prevalence of diabetes in patients with or without new-onset AF, which has also been noted in literature, regarding the population of patients with STEMI (1, 8, 13). At hospital discharge, the application of dual antithrombotic therapy and other therapy with beneficial influence on the prognosis of patients with STEMI (e.g., beta blockers and ACE inhibitors) did not significantly differ.

![Figure 1. Kaplan-Meier curves showing mortality during six-year follow-up according to the development of new-onset atrial fibrillation](image1)

![Figure 2. Receiver operating characteristic curve for estimated glomerular filtration rate](image2)
between the analyzed patients with new-onset AF and patients without new-onset AF.

The highest number of independent predictors for the occurrence of new-onset AF in patients with acute myocardial infarction, both in this study and in other studies, have been connected to ischemia (cardiac insufficiency at admission, IRA occlusion, postprocedural TIMI flow <3) and almost always, a smaller number of independent predictors are chronic conditions (comorbidities) (1, 2, 5, 20). In this study, reduced baseline kidney function was the only comorbidity which was independently associated with the occurrence of new-onset AF. In a study by Cosentino et al. (1) it was found that CKD (the only chronic comorbidity) was an independent predictor for the occurrence of new-onset AF in patients with STEMI and NSTEMI. As opposed to our study, patients with STEMI and NSTEMI were analyzed, and the authors of the abovementioned study did not analyze the mildly decreased values of eGFR, the value of eGFR <60 mL/min/m² was considered as CKD. The authors also have shown that both CKD and new-onset AF were independent predictors of long-term mortality in the analyzed patients; whereas in patients with moderate and severe CKD, mortality was greater if new-onset AF was also present. A study by Şerban et al. (2) found that CKD at admission (also the only chronic comorbidity) was an independent predictor for the occurrence of new-onset AF and AF occurring at patient admission, that is as the authors named it—"ischemia related AF". CKD at admission was a stronger independent predictor for the occurrence of new-onset AF than other known predictors of AF, such as cardiac insufficiency and left atrial diameter. The discriminative ability of eGFR for the occurrence of new-onset AF in the study by Şerban et al. (2) was almost identical to the finding of this study. However, creatinine clearance of <60 mL/min was considered as decreased kidney function in the aforementioned paper unlike in this study, and the prognostic impact of the degree of CKD was not analyzed, and only in-hospital mortality was analyzed. This study demonstrated that the impact of new-onset AF on mortality persisted in the long-term - six-year follow-up, as well. The prognostic impact of the early stages of CKD, that is mildly decreased eGFR values, on the occurrence of AF was analyzed more in studies examining CKD patient registers (13). In a study by Soliman et al. (13), analyzing AF occurrence in a population of patients with preterminal CKD, it was found that AF prevalence was two to three times higher in patients with mild-to-moderate CKD than that in the general population. In this study, the prognostic impact of mildly and mildly to moderately decreased eGFR on the occurrence of new-onset AF was lower than in the aforementioned study; this study, however, analyzed patients with STEMI, and the occurrence of new-onset AF in STEMI is also significantly influenced by mechanisms related to ischemia itself. As in the study by Soliman et al. (13), the prevalence of AF in mild-to-moderate CKD was similar to the prevalence in patients with terminal CKD, and the authors believed that the mechanisms through which decreased kidney function impacted the occurrence of AF were active in the earliest stage of kidney function deterioration (16).

The explanation for the predictive impact of CKD on the more frequent occurrence of AF as an infarction complication can be found in the more frequent existence of comorbidities, which are risk factors not only for CKD but also for AF (e.g., hypertension, diabetes mellitus, etc.), and also in the higher sensitivity of patients with CKD to the newly occurring hemodynamic changes (2, 15, 16). Patients with CKD are older, and age is also a risk factor for AF occurrence (17). However, in this study, declining kidney function was independently associated with the occurrence of new-onset AF along with the age of the patient. In addition, sympathetic over activity often occurs in abnormal kidney function (whether in acute kidney injury or in CKD) and is more pronounced with the decline in eGFR, thus facilitating the occurrence of AF in acute ischemia (1, 2). It has been shown that chronic inflammation, a typical characteristic of CKD from its earliest stages, is also an independent predictor of the occurrence of AF in infarction (1, 13).

Patients with new-onset AF have higher in-hospital mortality and a higher mortality in mid-term and long-term follow-up, which has been demonstrated by the results of numerous studies (1-4, 7, 8, 20). However, in a study by Topaz et al. (11), only previous AF was an independent predictor of long-term mortality in patients with STEMI, while the occurrence of new-onset AF was not, although there was a trend toward increased short-term and long-term mortality. The authors explained this finding by a relatively small number of patients with new-onset AF and a relatively small number of events during follow-up. In a large database of 106,708 patients with myocardial infarction, new-onset AF was associated with a 20% higher adjusted in-hospital mortality risk. However patients with AF at hospital admission had a mortality rate that was no different from that of patients with sinus rhythm, presumably a reflection of prior (persistent) AF as opposed to de novo AF (1, 21). In this study, in-hospital mortality in patients with AF was greater than in some other studies, (1-11) but the mortality during follow-up was mainly in correlation with the findings from literature (8, 9). The differences in short-term mortality could be explained by the differences in the inclusion of patients with AF into the study; this study excluded patients who had no medical data confirming any type of AF before admission. Therefore, we attempted to isolate patients in whom AF was a complication of ischemia itself and avoiding possible “overrating” of the occurrence of this type of arrhythmia in patients with STEMI.

**Clinical significance of the study:** As significant association of declining baseline kidney function with the occurrence of new-onset AF was registered even in patients with a mild decrease in eGFR, it is important to assess eGFR at hospital admission. This is necessary even in patients with normal values of serum creatinine (as patients with mildly decreased eGFR most often have normal values of serum creatinine) for identifying those among them who are at risk of developing new-onset AF, which will impact their prognosis. Further studies should analyze the potential benefit from therapy which has a positive impact on the prognosis of patients with STEMI, and it should
also investigate possible prophylactic antiarrhythmic therapy in this particular group of patients (2).

Study limitations
This study was observational, but controlled, prospective, and included consecutive patients with no missing data, limiting possible selection bias. Although patients with a medical history of AF were excluded, it was not possible to completely exclude the possible existence of (short-lasting) asymptomatic episodes of AF before admission. Repeated occurrence of AF during follow-up was not analyzed. Kidney function at hospital admission can be a chronic condition or an acute decline of kidney function. As the average time from the onset of complaints to hospital admission was around three hours, and as the blood for determining creatinine levels was taken immediately upon admission (before pPCI), we believe that STEMI related hemodynamic status could not have significantly influenced kidney function and that the values of eGFR in the patients included in this study were predominantly an indicator of a chronic state, rather than of a temporary worsening. In addition, patients with cardiogenic shock at admission were excluded from the study. The eGFR value <90 mL/min/m² was considered to be a reduced baseline eGFR, but this may solely be a reflection of age-related physiological decline in some patients. Kidney function was assessed with the use of the MDRD equation, which also has its limitations (22, 23). The rates of urinary albumin and protein excretion were not measured, which are factors that may influence the independent impact of kidney function on the risk of AF (17). In this study, patients were treated with clopidogrel; and none of them were treated with the more recently developed antiplatelet drugs (prasugrel and/or ticagrelor), and pPCI was predominantly performed using bare metal stents. Ticagrelor, prasugrel, and/or the new generation of drug-eluting stents or biodegradable polymers were not available for routine administration to patients at the time of their enrollment into the register, which may have influenced the prognosis of the analyzed patients. The study was not designed to evaluate whether changing pharmacological treatment would have an impact on the long-term outcome in the analyzed patients.

Conclusion
Reduced kidney function at admission was associated with the occurrence of new-onset AF in patients with STEMI treated with primary PCI, and the impact started already with mildly decreased eGFR and increased with its further decline. New-onset AF was an independent predictor of short-term and long-term mortality in the analyzed patients. Determining the value of eGFR at admission can help in early identification of patients who are at risk of the occurrence of new-onset AF and who may benefit from closer in-hospital monitoring, more frequent check-ups during follow-up, and more intensive secondary prevention.

Acknowledgments: The authors express their gratitude to the physicians and nurses of the coronary unit and catheterization laboratory who participated in the primary PCI program.

Conflict of interest: None declared.

Peer-review: Externally and internally peer-reviewed.

Author contributions: Concept – L.S., M.A.; Design – L.S.; Supervision – L.S., I.M.; Fundings – None; Materials – L.S.; Data collection &/or processing – L.S., S.S., G.K.; Analysis &/or interpretation – L.S., I.M., S.S., G.K.; Literature search – S.S., R.L., M.V.; Writing – L.S., R.L.; Critical review – L.S., I.M., M.A.

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