Mortality of patients with lone and idiopathic atrial fibrillation is similar to mortality in general population of Serbia

Mortalitet bolesnika sa lone i idiopatskom atrijalnom fibrilacijom nije veći od mortaliteta opšte populacije Srbije

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Abstract

Background/Aim. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in general population. The aim of the study was to compare all-cause mortality and cardiovascular mortality in patients with lone and idiopathic AF to correspondent mortality in general population of Serbia.

Methods. A longitudinal observational study included the patients with nonvalvular AF as the main indication for in-hospital and/or outpatient treatment in the Clinical Center of Serbia, during a period 1992–2007, if the latest date of first diagnosis of AF was early January 2003; in that way, the total follow-up could last at least 5 years (minimum 1 year prospectively), or until death. Principles of oral anticoagulation, heart rhythm and frequency control during the study period were conducted according to the latest international guidelines for diagnosis and treatment of AF in the study period. Lone and idiopathic AF were defined as AF in patients without any underlying disease, younger than 60 years (lone AF) or older (idiopathic AF). To compare mortality of the study population with mortality of general population we used the standardized mortality ratio (SMR) and chi-square test with p < 0.05 as a level of statistical significance. Results. Out of 442 patients with AF and no underlying disease, aged 47 ± 12.6 years, with mean follow-up of 11.5 ± 7.2 years, 12 patients (2.7%) died: 7 patients of non-cardiovascular causes and 5 patients (1.1%) of cardiovascular death. When compared to the general population of Serbia, all-cause mortality and cardiovascular mortality in the patients with lone and idiopathic AF were not higher than in general population (p < 0.05). Conclusion. All-cause mortality and cardiovascular mortality of patients with lone and idiopathic AF are similar to all-cause mortality and cardiovascular mortality in general population of Serbia.

Key words: mortality; atrial fibrillation; serbia.

Apstrakt

Uvod/Gilj. Atrijalna fibrilacija (AF) je najčešći poremećaj srčanog ritma u opštijoj populaciji. Gilj ovog rada bio je poređenje ukupnog i kardiovaskularnog mortaliteta bolesnika sa lone i idiopatskom AF sa ukupnim i kardiovaskularnim mortalitetom opšte populacije Srbije. Metod. Longitudinalnim opservacionim istraživanjem bili su obuhvaćeni bolesnici ambulantno i/ili bolnički lečeni zbog nevalvularne AF u Kliničkom centru Srbije u periodu 1992–2007, praćeni najmanje pet godina (i to prospektivno bar godinu dana) ili do smrtnog ishoda. Principi primene oralne antikoagulantne terapije, kontrole ritma i kontrole frekvencije srca usklađeni su sa najnovijim međunarodnim preporukama za dijagnostiku i lečenje AF u datom periodu studije. Lone i idiopatska AF definisane su kao AF kod osoba bez pridruženog srčanog ili drugog oboljenja, mladih, odnosno starijih od 60 godina. Za poređenje ukupnog i kardiovaskularnog mortaliteta studijske populacije sa mortalitetom stanovništva Srbije korišćen je χ² test slaganja, uz nivo značajnosti od p < 0.05. Rezultati. Od 442 bolesnika sa AF bez pridruženog oboljenja, prosečne starosti 47 ± 12,6 godina, sa prosečnim praćenjem 11,5 ± 7,2 godine, 12 bolesnika (2,7%) umrlo: sedam bolesnika od nekardiovaskularnih uzroka i pet (1,1%) kardiovaskularnom smrću. Poređenje ukupnog i kardiovaskularnog mortaliteta bolesnika sa lone i idiopatskom AF sa odgovarajućim mortalitetom ukupne populacije Srbije pokazalo je da nema statistički značajne razlike između njih (p < 0,05). Zaključak. Bolesnici sa lone i idiopatskom AF imaju sličan mortalitet kao ukupna populacija Srbije.

Key words: mortalitet; fibrilacija pretkomora; srbija.
Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in general population. However, AF is a heterogeneous disorder, with variable origin, clinical presentation and natural history. In the majority of patients, AF is accompanied by underlying heart disease, most frequently arterial hypertension. On the other hand, up to 30% of AF patients may be free of any known structural cardiopulmonary disease. Lone AF is defined as AF in otherwise healthy individuals not older than 60 years; if a patient is older than 60 years and has no underlying disease, AF is designated as idiopathic.

While the Framingham Heart Study identified AF as an independent predictor of increased risk of mortality, and the Paris Prospective Study found idiopathic AF to be associated with higher mortality compared to controls during a long-term follow-up, several clinical studies found lone and idiopathic AF to have similar overall survival as general population.

The aim of the present study was to compare all-cause mortality and cardiovascular mortality of patients with lone and idiopathic AF with correspondent mortality in general population of Serbia.

Methods

This longitudinal observational study included patients with nonvalvular AF as main indication for in-hospital and/or outpatient treatment in the Cardiology Clinic of Institute for Cardiovascular Diseases, Clinical Center of Serbia, during a period 1992–2007. The patients were included in the study if the latest date of their first diagnosed AF was early January 2003; in that way, a total follow-up lasted at least 5 years, with a minimum of 1 year of prospective follow-up, or until death.

The patients with acute causes of AF, advanced left ventricular systolic dysfunction (LVEF \( \leq 25\% \)), preexitation, known malignancy or any advanced chronic disease and the patients with poorly documented history of previous AF were not included in the study.

Diagnosis and treatment of AF were conducted according to the international standards valid in the given period of the study. The basic therapeutic approach throughout the whole study was to make every reasonable effort to restore and maintain sinus rhythm whenever possible. The principles of oral anticoagulation, rhythm control and frequency control during the study period were applied according to the latest international guidelines for diagnosis and treatment of AF in that study period.

Classification to lone and idiopathic AF was subsequently reexamined at the end of the study, based on ACC/AHA/ESC Guidelines on AF from 2006. After a detailed review of medical records of each patient in the study population, reclassification of AF was performed when needed.

A cause of death was obtained from medical records (hospital discharge letter, death certificate) combined with a detailed interview with a closest family member when death occurred out of hospital. A cause of death was subsequently classified according to EHRA (European Heart and Rhythm Association) classification, recently proposed for future studies on AF. Data on all-cause mortality and cardiovascular mortality of general population of Serbia for the period 1992–2006 were acquired from National Institute for Health Protection.

Continuous variables are shown as mean value ± standard deviation (SD). Categorical variables are given as counts with percentages. To compare mortality of the study population with mortality of general population we used standardized mortality ratio (SMR) and chi-square test with \( p < 0.05 \) as a level of statistical significance value, similarly to previously published papers.

Results

Out of 1,100 patients with nonvalvular AF, included in the study, 442 patients (40.2%) had AF without underlying disease: 377 patients (34.3%) were not older than 60 years, i.e., they had lone AF, while 65 patients (5.9%) had idiopathic AF.

The mean follow-up of the patients with lone and idiopathic AF was 11.5 ± 2.7 years. Baseline clinical and echocardiographic characteristics of these patients are shown in Table 1. The majority of patients had paroxysmal AF and normal left atrial anteroposterior diameter at baseline. However, in 1.1% of the patients AF was accompanied with transitory symptoms and signs of heart failure, despite normal left ventricular diameters and normal left ventricular systolic function.

| Baseline clinical and echocardiographic characteristics of the patients with lone and idiopathic atrial fibrillation (AF) |
|---|
| Age (years), mean ± SD | 47.0 ± 12.6 |
| Paroxysmal AF | 296 (67) |
| Persistent AF | 94 (21.3) |
| Permanent AF | 52 (11.8) |
| Left atrium ≤ 40 mm | 348 (78.7) |
| Tachyarrhythmia at presentation | 377 (85.3) |
| Heart failure at presentation | 5 (1.1) |
| Asymptomatic presentation of AF | 63 (14.3) |

Events recorded during the follow-up, including all-cause mortality and cardiovascular mortality are shown in Table 2. Transition to permanent AF occurred in slightly more than one third of patients with intermittent AF. The development of a new cardiac disease was documented in one forth of the patients with lone and idiopathic AF. The annual rates of any thromboembolic event, stroke and transitory ischemic episodes were quite low (0.44%, 0.21% and 0.18%, respectively), as well as the annual rates of all-cause mortality (0.25%) and cardiovascular mortality (0.10%).
Overall, 12 patients with lone and idiopathic AF died during the follow-up (2.7% of 442 patients with lone and idiopathic AF). Seven patients died of non-cardiovascular causes (4 patients from malignancy, 2 patients accidentally, 1 patient of chronic non-cardiac disease), while in 5 patients death was cardiovascular (2 patients died suddenly – one of them with clear evidence of acute myocardial infarction, 1 patient died of progressive congestive heart failure that occurred during the follow-up, 1 patient died of stroke and 1 patient died immediately after cardiac by-pass grafting surgery).

When compared to general population of Serbia, all-cause mortality and cardiovascular mortality in patients with lone and idiopathic AF did not significantly differ from correspondent expected mortalities, i.e. they were similar to all-cause mortality (Figure 1) and cardiovascular mortality in general population of Serbia (Figure 2).

Discussion

The main finding of the present study is that all-cause mortality and cardiovascular mortality of patients with lone and idiopathic AF in our study, after the mean follow-up of 11 years, were similar to correspondent mortalities in general population of Serbia. This is in concord with the findings in the population of 76 patients with lone AF reported by Jahangir et al. \(^1\) after the mean follow-up of 25 years. However, our study population was almost 6 times larger than their study population.

On the other hand, the Framingham Heart Study found AF to be an independent risk factor for mortality in general population with overt cardiac disease, and proposed that increased mortality was a direct consequence of AF, even in the absence of pre-existing cardiovascular disease\(^5\). However, Framingham study population was much older than our study population (mean 73.7 years vs. mean 47 years). Patients in the Paris Prospective Study had a similar mean age to our study population, but there were only 25 patients with AF and no underlying disease. These patients had similar non-cardiovascular death rate to controls, and higher cardiovascular death and all-cause death rates\(^9\).

The rates of transition to permanent AF, any thromboembolic event, stroke, all-cause mortality and cardiovascular mortality in our study population were quite similar to already mentioned study of Jahangir et al. \(^1\). Moreover, these investigators found that risk of adverse events in patients with lone AF increases with age or the development of hypertension.

There are more than a few reports suggesting that the risk of cardiovascular events in lone AF, including death, is age dependent and increases significantly with the development of hypertension, diabetes mellitus, congestive heart failure and coronary heart disease\(^12-16\). In our study population, almost 2/3 of deaths were non-cardiovascular, while the majority of cardiovascular deaths could be attributed to the development of new cardiovascular diseases during the follow-up. A post hoc analysis of ELAT Study, where the primary endpoint was the assessment of thromboembolic risk in

### Table 2

| Events recorded during the follow-up | Patients (n = 442) | n | % |
|-------------------------------------|--------------------|---|---|
| Progression to permanent AF*        | 128                | 32.0 |
| Any thromboembolic event            | 21                 | 4.8 |
| Stroke                              | 10                 | 2.3 |
| Transitory ischemic episode         | 9                  | 2.1 |
| New cardiac diseases                | 111                | 25.2 |
| Hypertension                        | 79                 | 17.9 |
| Coronary heart disease              | 7                  | 1.6 |
| Dilated cardiomyopathy              | 36                 | 8.1 |
| Tachycardiomyopathy                 | 28                 | 6.3 |
| Heart failure                       | 11                 | 2.5 |
| All-cause mortality                 | 12                 | 2.7 |
| Cardiovascular mortality            | 5                  | 1.1 |

\(^*128/390\) patients with intermittent (paroxysmal or persistent) atrial fibrillation (AF) at baseline

**Fig. 1 – All-cause mortality in the patients with lone and idiopathic atrial fibrillation (AF), and in general population of Serbia.**

**Fig. 2 – Cardiovascular mortality in the patients with lone and idiopathic atrial fibrillation, and in general population of Serbia.**

AF patients, revealed that all-cause mortality of patients with AF was 1.4 times higher than mortality of general population, mainly because of the concomitant congestive heart failure. Stollberger et al. \(^17\) concluded that prognosis of patients with AF highly depends on underlying cardiovascular comorbidity. A similar conclusion was driven from the results of SCAF study, when all-cause mortality of patients
with paroxysmal AF was analyzed. We have also previously reported that all-cause mortality and cardiovascular mortality in overall population of AF patients are higher than such mortalities in general population of Serbia. Obviously, active treatment of present cardiovascular diseases and, even more importantly, prevention of development of new cardiovascular diseases during the follow-up can significantly improve the prognosis of patients with AF.

This study is subject to limitations inherent in observational studies and selection bias is an important consideration. Although this was a non-directed study and a choice of AF treatment was left to a responsible doctor, we believe that a tertiary nature of our hospital ensured a proper decision-making, which makes our study comparable to other similar investigations. On the other hand, a tertiary center experience may not completely reflect the overall treatment approach and a long-term outcome of patients with lone and idiopathic AF in clinical practice.

Conclusion

All-cause mortality and cardiovascular mortality of patients with lone and idiopathic AF are similar to all-cause mortality and cardiovascular mortality in general population of Serbia. However, active treatment of rhythm disorder and proper prevention of complications of AF are necessary. Moreover, patients with lone and idiopathic AF need close monitoring for prevention or early recognition of the development of new cardiovascular diseases during follow-up.

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