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Sex differences in long-term survival following cardiac surgery in patients with underlying atrial fibrillation

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INTRODUCTION

Atrial fibrillation (AF) remains the most common cardiac rhythm disorder, and due to its persistently growing trend, especially in the elderly population, it has become the new epidemic of the XXI century [1]. Based on a large, nationwide study AF increases the risk of all-cause death by 3.7-fold and the risk due to cardiovascular death by 5 times compared with the general population [2]. As for the sex differences in the AF influence, a meta-analysis of cohort studies reported that AF is a stronger risk factor for cardiovascular disease, as well as mortality in women rather than in men [3]. The prevalence of AF before cardiac surgery reaches up to almost 29% of patients [4]. Many studies observed that underlying AF has an impact on short- and long-term outcomes after various cardiac procedures. In patients with concomitant aortic

valve replacement and coronary artery bypass graft surgery (CABG), AF was independently associated with reduced mid-term survival [5]. It also substantially reduces long-term survival after a single CABG, which prompts to performance of concomitant surgical ablation [6]. It is even suggested that AF should be considered as a high-risk marker of complications after the surgery [7]. However, there is a paucity of data that reports on sex differences among patients with preoperative AF undergoing cardiac surgery including the sex comparison of survival. The aim of this analysis was to assess sex differences in long-term survival following cardiac surgery in patients with underlying AF.

METHODS

Data were collected in a retrospective fashion from the Polish National Registry of Cardiac Surgery Procedures registry (KROK) (available at: www.krok.csioz.gov.pl). The registry is an ongoing, nationwide, multi-institutional registry of heart surgery procedures in Poland; the details on registry conception and design were described previously [8]. Due to anonymization of registry data and retrospective nature of the study both patient consent and ethics committee approval respectively were waived. The registry included all adult patients undergoing heart surgery for whatever reason between January 1, 2018 and March 31, 2020 and evidence of any type of pre-operative AF. Post-operative AF was not recorded and therefore not considered. For patients undergoing heart surgery, we considered and reported 3 categories of variables: (1) baseline demographics (2) surgical variables: urgency, operative technique (3) postprocedural complications (see Figure 1). All diagnoses of the variables studied were made based on current guidelines and those stated in EUROSCORE II. In the case of hypertension — based on guidelines stated in the CHA_2DS_2-VASc score. Diagnoses were made by KROK investigators and were not verified afterward. Normal distribution was assessed using a Shapiro–Wilk test. Descriptive analyses were represented as a median (Me) with interquartile range (IQR) for continuous variables, and for categorical variables as a number (n) of occurrences (%). The statistical significance of differences between the two groups was determined using the χ^2 and Mann–Whitney U. The estimated survival probability was presented graphically by Kaplan–Meier curves. The prognostic relevance of sex regarding the prediction of endpoints was estimated using univariable and multivariable Cox regression analysis. The multivariable Cox regression model included the variables with P <0.05 in the univariable model. The primary endpoint was death from any cause reported up to 4-year follow-up for the comparison of women vs men. Follow-up status with respect to all-cause mortality is validated by the Polish National Health Fund and incorporated into the KROK registry. For all analyses, we set the

level of statistical significance at P <0.05. All statistical analysis was performed using Stata Statistical Software (StataCorp, 2023, version 18, TX, US).

RESULTS AND DISCUSSION

The basic characteristics of patients and treatment data are shown in Figure 1. The final study cohort consisted of 4989 patients with a majority of men at 65.1% and a median age of 69 years (IQR 63–74). The male population was characterized by a higher prevalence of risk factors for coronary artery disease such as hyperlipidemia and hypertension, as well as the greater prevalence of chronic coronary syndrome and previous myocardial infarction itself. The female population was older, had a higher left ventricular ejection fraction, poorer renal function, and a higher prevalence of severe pulmonary hypertension. Moreover, women had a significantly higher score in a EUROSCORE II model (Me = 3.79 [IQR, 2.10–6.90] vs. 2.56 [1.44–5.00]; P <0.001).

As for the operative characteristics, men were more frequently undergoing single-CABG surgery (16.4% [n = 286] vs. 37.4% [n = 1215]; P <0.001), whereas women more often underwent complex procedures. The female population was more often treated with left atrial appendage occlusion (22.01% vs. 17.54%; P <0.001), no sex differences were shown in the case of ablation. No differences were observed in terms of surgery type (urgent, emergency, salvage) between the sexes.

Considering the overall in-hospital outcomes in our study group, the female cohort more often had after-procedural complications (27.07% [n = 471] vs. 23.08% [n = 750]; P = 0.002).

When divided by specific complication, there were no differences between the sex groups except for sternal infections, which were more prevalent in men, and respiratory failure, which was more common in the female population (9.83% [n = 171] vs. 7.73% [n = 251]; P = 0.01).

During the initial period of the observation, the female population is characterized by statistically significant poorer survival than men group (90-days death: 11.44% [n = 199] vs. 8.93% [n = 290]; $HR_{F\ vs.\ M}$ = 1.233 [95% CI, 1.029–1.477]; P <0.001). This trend reverses after the second year of follow-up (HR for 0–760 days 1.433 [95% CI, 1.252–1.640]; P <0.001 vs. HR 760–1460 days 0.718 [95% CI, 0.109–0.907]; P = 0.005). Differences in factors that affect long-term prognosis were also however, there were no differences between the both sexes.

In our opinion, the initial poorer prognosis of the women's group stems from a higher perioperative risk, which is reflected in the EUROSCORE score. Several studies so far reported that women achieve higher EUROSCORE compared to men [8–10]. Trienekens et al. [9]

observed that although women are at higher risk of early mortality, the female sex is not an independent risk factor itself. The potential predictive underestimation of EUROSCORE in patients with AF in our cohort is negligible due to AF being the baseline criterion for inclusion in this study [11]. Results from the United Kingdom National Adult Cardiac Surgery Audit on the overall population are consistent with our analysis showing an increased risk of short-term mortality after cardiac surgery in women [8]. Interestingly, in terms of after-procedural complications, females in the United Kingdom also had sternal infections more often than males. In our opinion, the shift in mortality that occurs over the second year may result from better long-term care in the female group and better compliance with treatment recommendations [12]. With men having a worse prognosis at follow-up, greater emphasis on secondary prevention and close follow-up to better manage AF and co-morbidities seems essential. Extended follow-ups and statistical analyses are necessary for re-evaluating prevailing assumptions.

In conclusion, the female population is characterized by poorer survival after cardiac surgery and this trend reverses after 2 years of follow-up. Differences in short-term and long-term mortality between the sexes may be due to the different courses of AF in each sex.

The paper has the typical limitations of large retrospective registry studies. We recorded <5% of missing data; moreover, the type of AF was not included in the patient analysis.

Article information

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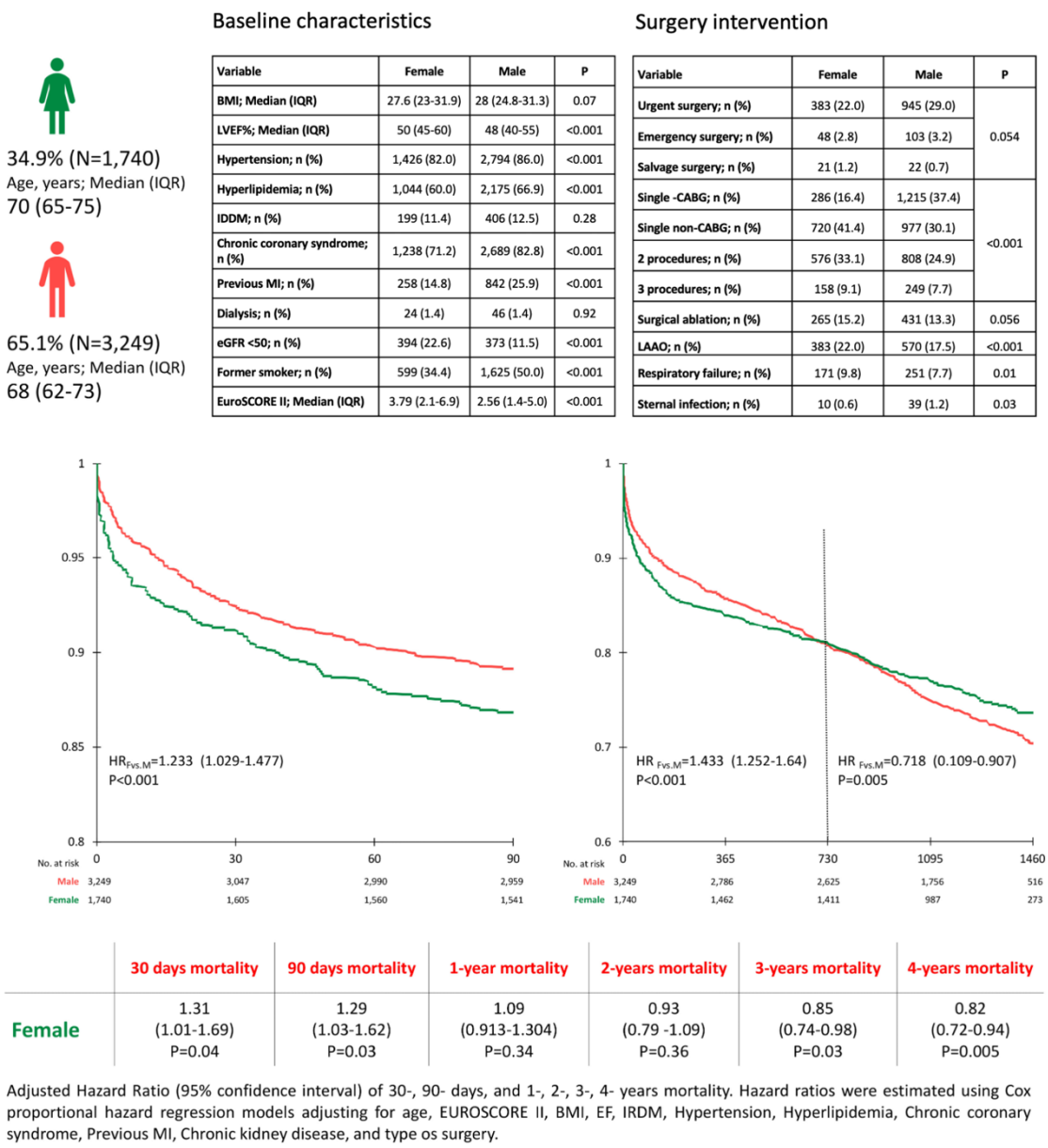

Variable	Female	Male	P
BMI; Median (IQR)	27.6 (23-31.9)	28 (24.8-31.3)	0.07
LVEF%; Median (IQR)	50 (45-60)	48 (40-55)	<0.001
Hypertension; n (%)	1,426 (82.0)	2,794 (86.0)	<0.001
Hyperlipidemia; n (%)	1,044 (60.0)	2,175 (66.9)	<0.001
IDDM; n (%)	199 (11.4)	406 (12.5)	0.28
Chronic coronary syndrome; n (%)	1,238 (71.2)	2,689 (82.8)	<0.001
Previous MI; n (%)	258 (14.8)	842 (25.9)	<0.001
Dialysis; n (%)	24 (1.4)	46 (1.4)	0.92
eGFR <50; n (%)	394 (22.6)	373 (11.5)	<0.001
Former smoker; n (%)	599 (34.4)	1,625 (50.0)	<0.001
EuroSCORE II; Median (IQR)	3.79 (2.1-6.9)	2.56 (1.4-5.0)	<0.001

Variable	Female	Male	P
Urgent surgery; n (%)	383 (22.0)	945 (29.0)	0.054
Emergency surgery; n (%)	48 (2.8)	103 (3.2)	
Salvage surgery; n (%)	21 (1.2)	22 (0.7)	
Single -CABG; n (%)	286 (16.4)	1,215 (37.4)	<0.001
Single non-CABG; n (%)	720 (41.4)	977 (30.1)	
2 procedures; n (%)	576 (33.1)	808 (24.9)	
3 procedures; n (%)	158 (9.1)	249 (7.7)	
Surgical ablation; n (%)	265 (15.2)	431 (13.3)	0.056
LAAO; n (%)	383 (22.0)	570 (17.5)	<0.001
Respiratory failure; n (%)	171 (9.8)	251 (7.7)	0.01
Sternal infection; n (%)	10 (0.6)	39 (1.2)	0.03

	30 days mortality	90 days mortality	1-year mortality	2-years mortality	3-years mortality	4-years mortality
Female	1.31 (1.01-1.69) P=0.04	1.29 (1.03-1.62) P=0.03	1.09 (0.913-1.304) P=0.34	0.93 (0.79 -1.09) P=0.36	0.85 (0.74-0.98) P=0.03	0.82 (0.72-0.94) P=0.005

Adjusted Hazard Ratio (95% confidence interval) of 30-, 90- days, and 1-, 2-, 3-, 4- years mortality. Hazard ratios were estimated using Cox proportional hazard regression models adjusting for age, EUROSCORE II, BMI, EF, IRDM, Hypertension, Hyperlipidemia, Chronic coronary syndrome, Previous MI, Chronic kidney disease, and type os surgery.

Figure 1. Characteristics of the study participants

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; EF, ejection fraction; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IRDM, insulin-requiring diabetes mellitus; LAAO, left atrial appendage occlusion; LVEF, left ventricle ejection fraction; MI, myocardial infarction