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ORIGINAL RESEARCH

All-Cause Mortality of Atrial Fibrillation and Heart Failure in the Same Patient: Does the Order Matter?

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ABSTRACT

***Introduction*:** Atrial fibrillation (AF) and heart failure (HF) often coexist due to the common elements of the pathomechanism they share. The potential significance of the order these entities present in the same patient is ill-defined. Herein, we report our results from a nationwide database on the occurrence of various sequences AF and HF may present, the time delays between the two conditions and all-cause mortality associated with different scenarios.

***Methods*:** Patients diagnosed with both AF and HF between 2015 and 2021 were enrolled from the Hungarian National Health Insurance Fund (NHIF) database. The order the two entities followed each other, and the time delay in between were registered. Median survival rates were calculated in AF → HF; HF → AF and simultaneous scenarios.

***Results*:** A total of 109,075 patients were enrolled: 29,937 with AF → HF, 38,171 with HF → AF, and 40,967 diagnosed simultaneously. Time delays between AF → HF and HF → AF were 6 and 10 months, respectively. The median survival was 46 months in the AF → HF, 38 months in the HF → AF, and 21 months in the simultaneous group. Patients with HF → AF, and with simultaneous presentations had 5% and

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16% greater mortality risk as compared to the AF→HF sequence, with hazard ratios (95% confidence intervals) of 0.95 (0.93–0.97) and 0.84 (0.82–0.85), respectively ($P<0.0001$).
Conclusions: HF occurred significantly earlier after the diagnosis of AF than vice versa. Patients diagnosed simultaneously had the worst, while the AF→HF sequence had the best prognosis. These data should have implications for the intensification of monitoring and therapy in different scenarios.

Keywords: Atrial fibrillation; Heart failure; Mortality risk; Real-world evidence

Key Summary Points

Why carry out this study?

Atrial fibrillation and heart failure are cardiovascular epidemics with a high mortality rate and burden on the healthcare system.

The order atrial fibrillation and heart failure present might be predictive of survival, however available evidence is limited.

What was learned from this study?

A nationwide study including more than 100,000 patients was conducted to test whether the order atrial fibrillation and heart failure present in the same patient is predictive of all-cause mortality. Further, the time delay between the occurrences of these conditions was also examined.

The presentation of heart failure in a patient with preexisting atrial fibrillation was associated with significantly better prognosis as compared with the opposite order. Patients diagnosed with atrial fibrillation and heart failure simultaneously had strikingly poor prognosis.

The order atrial fibrillation and heart failure meet in the same patient should be considered as it may have significant implications for the management of patients including the intensification of available therapy and tighter monitoring during follow-up.

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are global cardiovascular epidemics with significant morbidity, mortality, and a high burden on the healthcare system in many countries [1, 2]. Both conditions are related to aging and share many comorbidities and elements of the pathophysiology promoting their co-existence in the same patient [3, 4]. Furthermore, concurrent AF and HF are associated with worse outcome than any of the two conditions alone. The presence of AF is associated with an increased risk of death across the whole spectrum of HF, classified according to left ventricular ejection fraction (LV EF) [5, 6]. Data suggest that the order AF and HF present in the same patient might predict different outcomes. In the DIAMOND study new-onset AF developed later during HF progression but not baseline AF was associated with increased all-cause mortality [7]. AF developing during follow-up in HF patients also predicted worse outcomes in the CHARM registry [8]. Similar findings of observational studies have also been reported [9, 10]. However, no relevance of the AF-HF sequence was demonstrated in the COMET [11] and PRIME II trials [12]. In more recent publications, paroxysmal and especially new-onset AF resulted in worse outcome in patients with existing HF as compared to preexisting and persistent forms of the arrhythmia [13, 14]. These observations have also been confirmed by recently published data from a nationwide Danish database based on more than 49,000 patients with the diagnosis of both AF and HF: significantly better survival was demonstrated when AF was diagnosed before HF than vice versa [15].

Herein, we conducted a nationwide, retrospective, longitudinal study to determine the occurrence of the various sequences AF and HF may present in the same patient, the time delays between the two conditions and all-cause mortality associated with the three different scenarios: AF→HF, HF→AF and simultaneous presentation. Further, we also analyzed the potential influence of sex and age on all these endpoints.

METHODS

Study Cohort

We searched the database of the National Health Insurance Fund (NHIF) to identify patients who were diagnosed with both AF and HF between January 1, 2015 and September 30, 2021. As our country has a single state-owned insurance company covering both in-hospital and outpatient activities, the data of the whole population of interest were captured. Health care costs are covered by NHIF based on its administrative database. In order to get financial reimbursement, health care providers need to enter the code of the primary diagnosis a patient was treated for using the 10th review of International Classification of Diseases (ICD). In this research, patients with at least two occurrences of ICD codes both for AF (I48) and for HF (I50, I11, I13, I25, I42, I46, I47, I09, J81) within a period of 30–365 days either as out- or inpatient during the study period were considered for the study. These criteria were applied to avoid miscoding and to ensure that these patients were under regular medical care for AF and HF. In addition, to ensure that only newly diagnosed AF and HF cases were included in the analysis, a 2-year screening period was applied between 2013 and 2015 and patients with even one diagnosis code of either AF or HF within this time period were excluded (Fig. 1). Anonymized data provided by the National Health Insurance Fund for this research did not contain any personal information which could be used to identify the patients. The study protocol was reviewed and confirmed by the National Health Insurance Fund (identification number: I043/125/2021) and they provided us the anonymized database which was later used for statistical analysis.

Data Analysis and Study Periods

Our study had three main analyses with slightly different time windows

1. We determined the *occurrences of the different sequence scenarios* (AF → HF, HF → AF or simultaneous) for patients newly diagnosed with AF and HF. For this analysis, patients identified with both diagnoses during the whole study period (between January 2015 and the end of September 2021) were considered. The index date of each diagnosis was defined as the date of the first ICD record for the patient during the study period.
2. The *time delays between the diagnoses of the two entities* were determined as the median time in months elapsed until HF presented after the first diagnosis of AF, or AF presented after the first diagnosis of HF. The inclusion time window for this analysis was also the whole study period as above.
3. The time window for *mortality analysis was abbreviated to exclude the potential influence* of the COVID-19 pandemic. In our country, the number of COVID-19-related deaths showed a significant rise only after September 30, 2020. Accordingly, the end of follow-up to capture all-cause death was set until this date. Further, to ensure that all patients had an at least 6 months follow-up, the final date of enrollment for mortality analysis was March 31, 2020. This narrower time window explains the lower number of patients considered for mortality analysis.

Age and sex group analyses were performed in each part of the study for age groups below 65 years, between 65 and 79 years, and above 80 years.

Statistics

Categorical data were presented as frequencies with percentages, and statistical differences were tested with chi-squared tests. Continuous variables were presented as mean with standard deviation, and statistical difference was tested using Welch's *t* test. Baseline characteristics were compared at the index time, which was defined as the time of first diagnosis of AF or HF. The time from the first diagnosis to the second appearance was plotted on Kaplan–Meier curves and compared with the log-rank test. Survival after the second diagnosis was analyzed using Cox regression. The result was considered significant at $P<0.05$. R statistical software (version 4.2.0) was used for statistical analyses. Data were corrected for age and sex

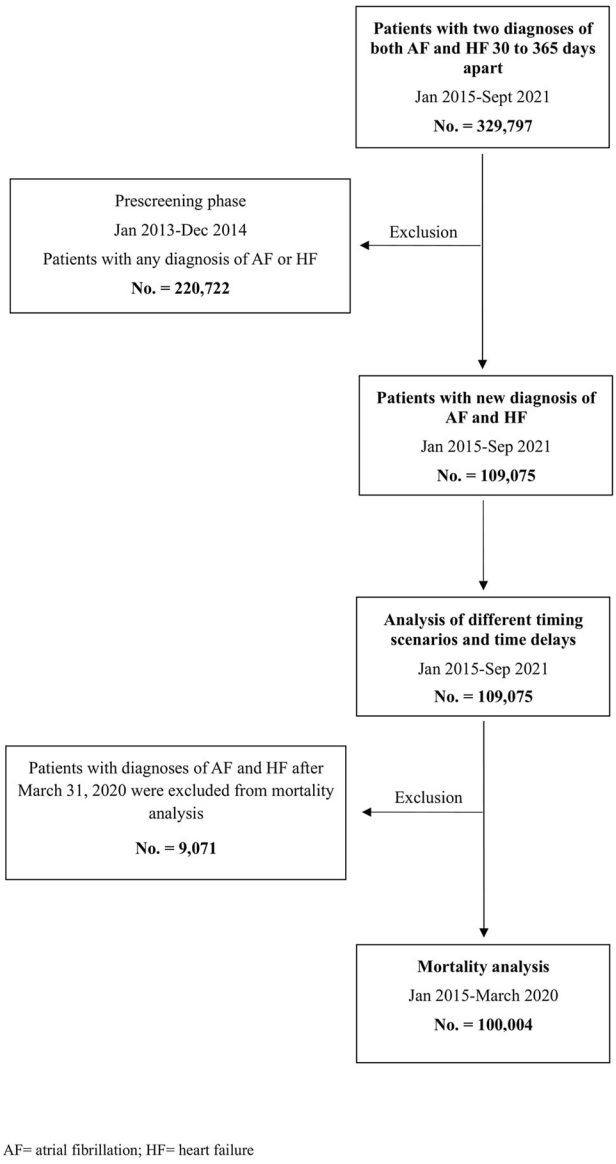


Fig. 1 Patient identification scheme

for analyses of mortality and time delays between the diagnoses of the two entities.

RESULTS

Occurrence, Sex, and Age Distribution According to the Different Timing Scenarios

A total of 109,075 patients were enrolled. AF was diagnosed first and was followed by HF in 29,937 patients (AF → HF group), while the diagnosis of HF was followed by AF in 38,171 patients (HF → AF group) ($P = 0.2340$). The two conditions were diagnosed at the same time in 40,967 patients (simultaneous group) ($P < 0.0001$). In the AF → HF and HF → AF groups representation of the sexes was similar (48.9% male/51% female vs. 49.5% male/50.5% female; $P = 0.1407$), while the female sex was overrepresented (53.2%) in simultaneously diagnosed cases ($P < 0.0001$). The ratio of patients older than 80 years was also

significantly higher in the simultaneous group ($P<0.0001$) (Table 1).

Survival Analysis

A total of 100,004 patients were included in the survival analysis. The sequence was AF→HF in 26,398 patients, HF→AF in 32,639 patients, and 40,967 patients were diagnosed simultaneously.

The Kaplan–Meier analysis of the study population resulted in a median survival of 46 months in the AF→HF, 38 months in the HF→AF, and 21 months in the simultaneous group. Patients with HF→AF, and those diagnosed simultaneously had 5% and 16% greater mortality risk compared to the AF→HF sequence, with hazard ratios (HR) (95% confidence intervals [CI]) of 0.95 (0.93–0.97) and 0.84 (0.82–0.85), respectively ($P<0.0001$). The hazard ratio for mortality in the simultaneous group was 12% greater (HR=0.88; 95% CI 0.86–0.90, $P<0.0001$) compared to the HF→AF sequence (Fig. 2).

The Kaplan–Meier analysis of different age subgroups was also performed (Fig. 3a–c). In the less than 65-year-old age cohort the mortality of AF→HF group was significantly lower as compared to the HF→AF and to the simultaneous groups with HRs (95% CI) of 0.75 (0.70–0.81) and 0.71 (0.67–0.76), respectively ($P<0.0001$). There was no significant difference between the HF→AF and the simultaneous groups (HR=0.95; 95% CI 0.89–1.00, $P=0.0693$) (Fig. 3a).

In the 65–79-year-old age group the survival of the AF→HF group was 63 months, significantly

Table 1 Age and sex distribution of patients with the different orders of presentation

	AF first	HF first	Simultaneous	AF vs. HF first *P* value	AF first vs. simultaneous *P* value	HF first vs. simultaneous *P* value
Total *N*	29,937	38,171	40,967			
Age (mean ± SD)	72.1 ± 10.88	71.9 ± 10.92	74.63 ± 11.17	0.0175	< 0.0001	< 0.0001
Sex				0.1407	< 0.0001	< 0.0001
Female, *n* (%)	15,285 (51.06)	19,272 (50.49)	21,801 (53.22)	0.1407	< 0.0001	< 0.0001
Male, *n* (%)	14,652 (48.94)	18,899 (49.51)	19,166 (46.78)	0.1407	< 0.0001	< 0.0001
Age group total, *n* (%)				0.2340	< 0.0001	< 0.0001
≤ 64	6882 (23.0)	8976 (23.52)	7638 (18.64)	0.1063	< 0.0001	< 0.0001
65–79	15,138 (50.57)	19,236 (50.39)	17,861 (43.6)	0.6561	< 0.0001	< 0.0001
≥ 80	7917 (26.43)	9959 (26.09)	15,468 (37.76)	0.2959	< 0.0001	< 0.0001
Age group female, *n* (%)				0.7409	< 0.0001	< 0.0001
≤ 64	2213 (14.48)	2846 (14.77)	2008 (9.21)	0.4499	< 0.0001	< 0.0001
65–79	7783 (50.92)	9796 (50.83)	9086 (41.68)	0.8695	< 0.0001	< 0.0001
≥ 80	5289 (34.6)	6630 (34.4)	10,707 (49.11)	0.6972	< 0.0001	< 0.0001
Age group male, *n* (%)				0.4932	< 0.0001	< 0.0001
≤ 64	4669 (31.87)	6130 (32.44)	5630 (29.37)	0.2680	< 0.0001	< 0.0001
65–79	7355 (50.2)	9440 (49.95)	8775 (45.78)	0.6520	< 0.0001	< 0.0001
≥ 80	2628 (17.93)	3329 (17.61)	4761 (24.84)	0.4448	< 0.0001	< 0.0001

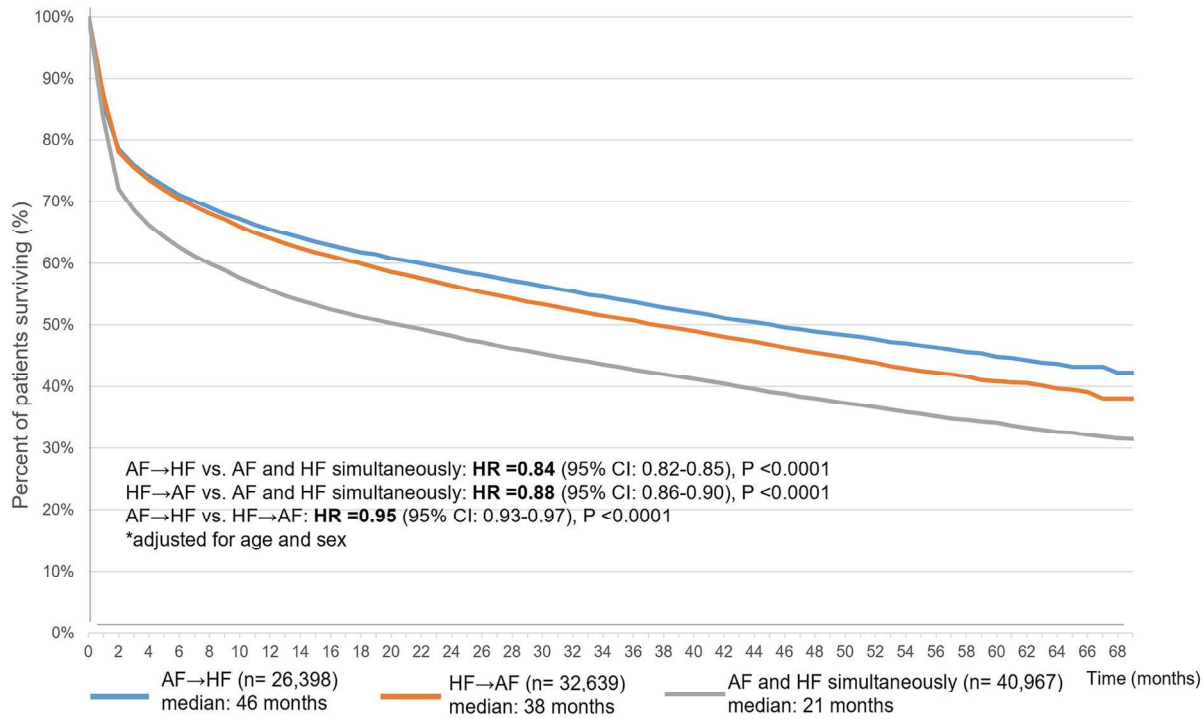
AF atrial fibrillation, *HF* heart failure

better compared to the HF → AF (51 months) and simultaneous groups (40 months), with a mortality risk reduction of 10% (HR = 0.90; 95% CI 0.87–0.94, $P < 0.0001$) and 22% (HR = 0.78; 95% CI 0.76–0.81, $P < 0.0001$), respectively. Further, the survival of the HF → AF vs. simultaneous group was also better, with a 13% lower mortality risk (HR = 0.87; 95% CI 0.84–0.89, $P < 0.0001$) (Fig. 3b).

In the elderly (≥ 80 years old) patient population the HF → AF group had a median survival of 7 months, and a 16% mortality risk reduction compared to the simultaneous group (HR = 0.84; 95% CI 0.81–0.86, $P < 0.0001$); the AF → HF group had a median survival of 6 months and an 11% mortality risk reduction compared to the simultaneous group (HR = 0.89; 95% CI 0.86–0.92, $P < 0.0001$), where the median survival was 4 months (Fig. 3c).

In the AF → HF, as well as in the HF → AF scenarios the mortality of male patients was significantly higher in the less than 64-year-old and 65 to 79-year-old age groups. The overall relative risk reduction of female patients was 15% (HR = 0.85; 95% CI 0.82–0.88, $P < 0.0001$), respectively 10% (HR = 0.90; 95% CI 0.88–0.93, $P < 0.0001$) (Figs. 4, 5).

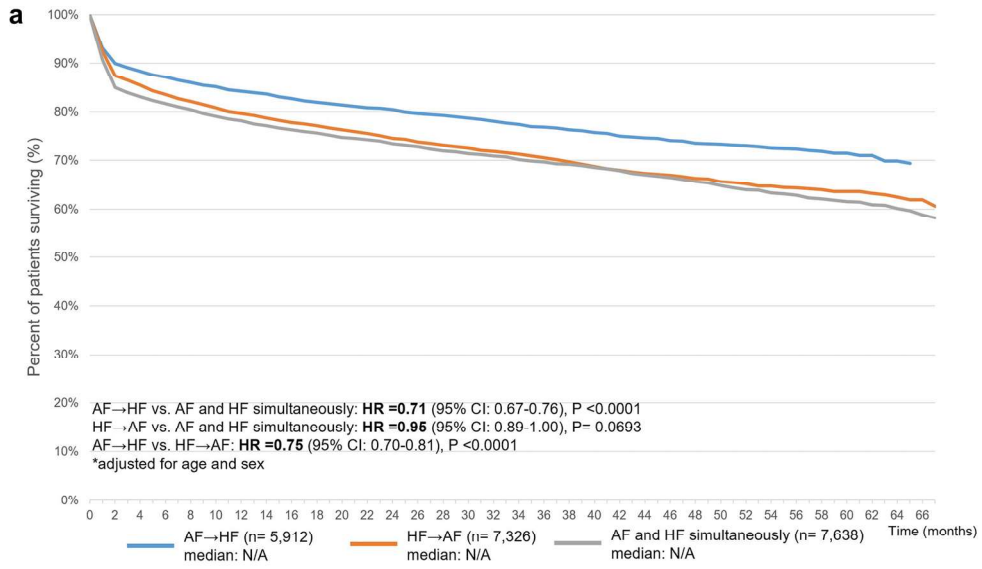
When the two entities were diagnosed at the same time the mortality risk reduction of female patients was manifest in the 65–79-year-old age group, also the overall mortality risk of female patients was lower (HR = 0.94; 95% CI 0.91–0.96, $P < 0.0001$) (Fig. 6).



	0 months	24 months	48 months	68 months
AF→HF	26,398	10,788	3,396	140
HF→AF	32,639	12,355	3,463	109
Simultaneous	40,967	15,674	6,456	620

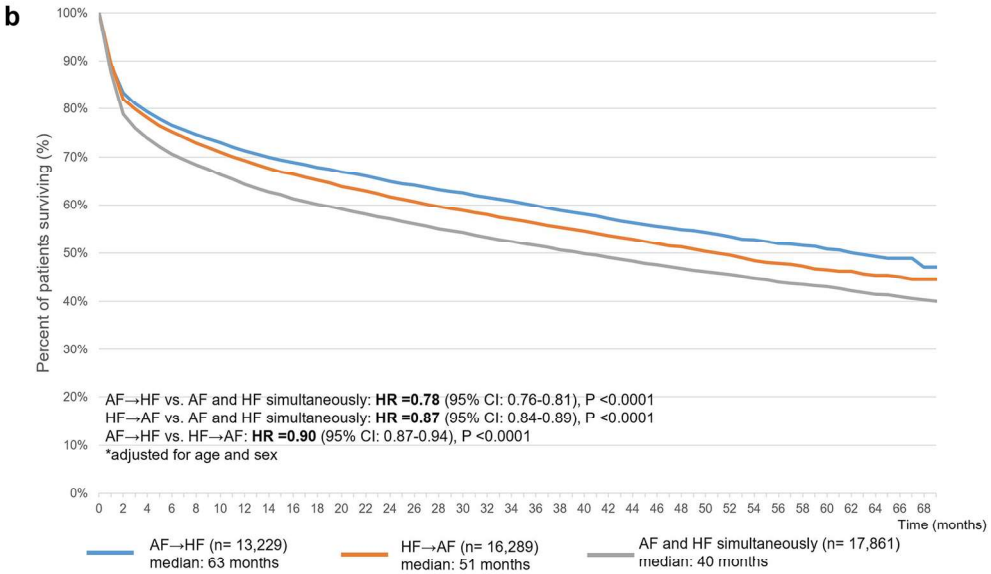
AF= atrial fibrillation; HF= heart failure

Fig. 2 Kaplan–Meier curves of overall survival according to sequence scenarios



	0 months	24 months	48 months	66 months
AF→HF	5,912	2,991	913	82
HF→AF	7,326	3,275	876	46
Simultaneous	7,638	3,969	1,583	232

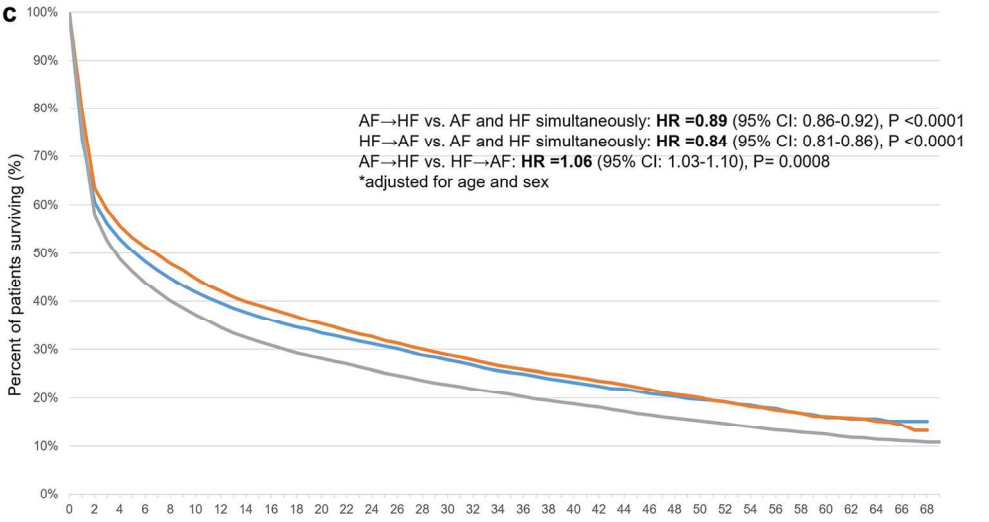
AF= atrial fibrillation; HF= heart failure; N/A= not available



	0 months	24 months	48 months	68 months
AF→HF	13,229	5,713	1,778	25
HF→AF	16,289	6,401	1,770	19
Simultaneous	17,861	7,849	3,320	180

AF= atrial fibrillation; HF= heart failure

Fig. 3 **a** Kaplan–Meier curve of survival below age 65 according to different sequence scenarios. **b** Kaplan–Meier curve of survival between 65–79 years according to different sequence scenarios. **c** Kaplan–Meier curve of survival over 79 years according to different sequence scenarios



	0 months	24 months	48 months	68 months
AF→HF	7,257	1,709	497	27
HF→AF	9,024	2,187	560	36
Simultaneous	15,468	3,397	1,245	50

AF= atrial fibrillation; HF= heart failure

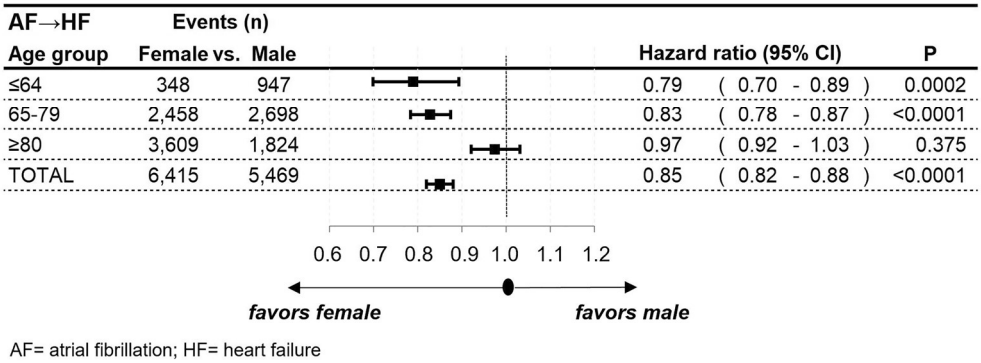
Fig. 3 continued

The Delay Between the Diagnoses of AF and HF

AF was diagnosed first followed by HF after 6 months (median follow-up 156 days), while HF was diagnosed first followed by AF after 10 months in both male and female patients (median follow-up 274 days) ($P < 0.0001$) (Fig. 7).

HF appeared following AF after a median time of 4 months in the ≥ 80-year-old group, significantly earlier compared to the ≤ 64-year-old ($P < 0.0001$), and 65–79-yeard-old age groups ($P < 0.0001$) (6, respectively 7 months) (Fig. 8).

AF appeared following HF after a median time of 7 months in the ≥ 80-year-old age group, significantly earlier compared to the 65–79 ($P < 0.0001$), and ≤ 64-year-old age groups



AF= atrial fibrillation; HF= heart failure

Fig. 4 Forest plot of mortality according to age and sex group when AF is followed by HF

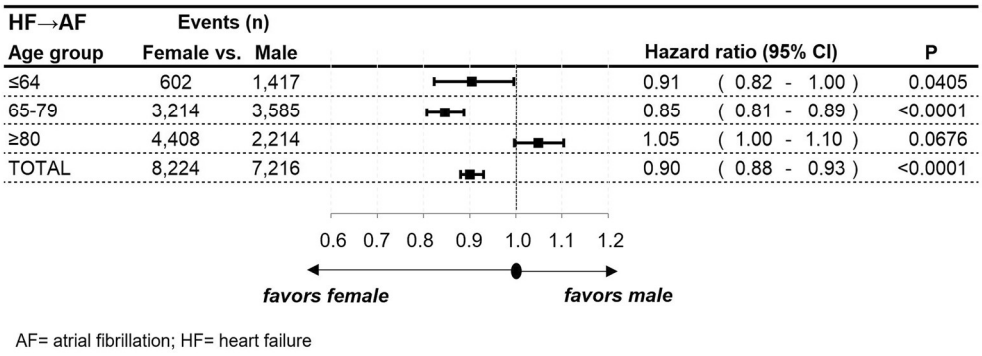


Fig. 5 Forest plot of mortality according to age and sex group when HF is followed by AF

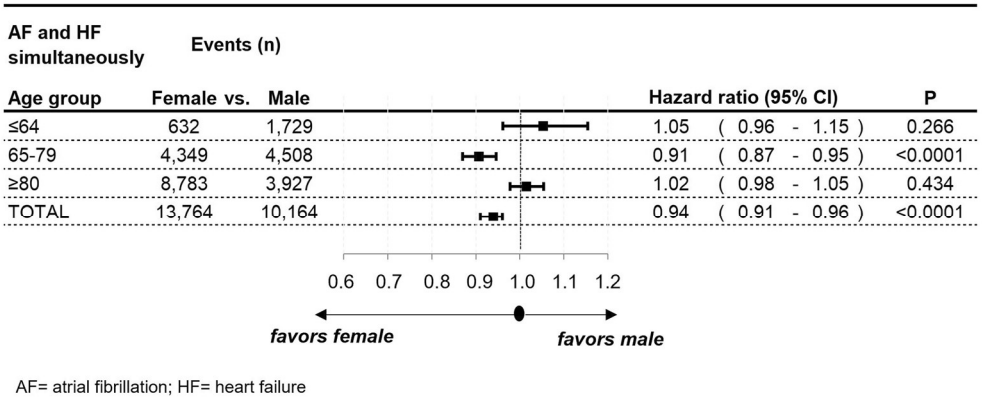


Fig. 6 Forest plot of mortality according to age and sex group when AF and HF are diagnosed at the same time

($P<0.0001$) (11, and 12 months, respectively) (Fig. 9).

Overall, HF occurred significantly earlier after AF than vice versa across all age groups: 4 vs. 7 months in the >80-year-old age groups, 7 vs. 11 months in the 65–79-year-olds, and 6 vs. 12 in the ≤64-year-olds.

DISCUSSION

AF and HF are considered cardiovascular "epidemics" of these days affecting millions of people. Both are chronic disorders, and patients are usually managed for years as out- or inpatients under the care of family physicians, internists, cardiologists, or subspecialists such as cardiac electrophysiologists or heart failure specialists. Even though the coexistence of AF and HF in the same patient is a common problem, the information on the clinical relevance of the order these entities present is limited.

In our study, the most common timing scenario was the simultaneous presentation of AF and HF, followed by HF → AF and the AF → HF sequences. Patients with simultaneous presentation included more women and patients from the oldest (80+) cohort as compared with the two other groups. Although mixed results have been published in the few studies with similar data available (Table 2), a relatively even distribution was found with a significant representation of each timing scenario.

In the whole cohort including 100,004 patients with mortality data available Kaplan–Meier survival curves separated

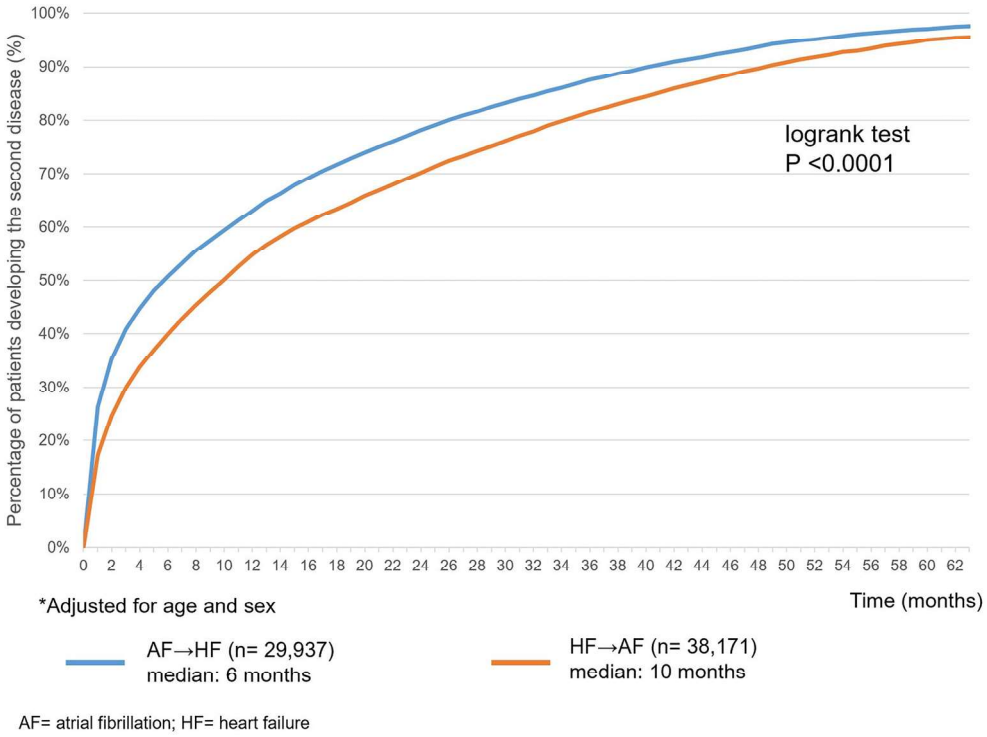


Fig. 7 Delay between the first and second diagnosis in the two scenarios

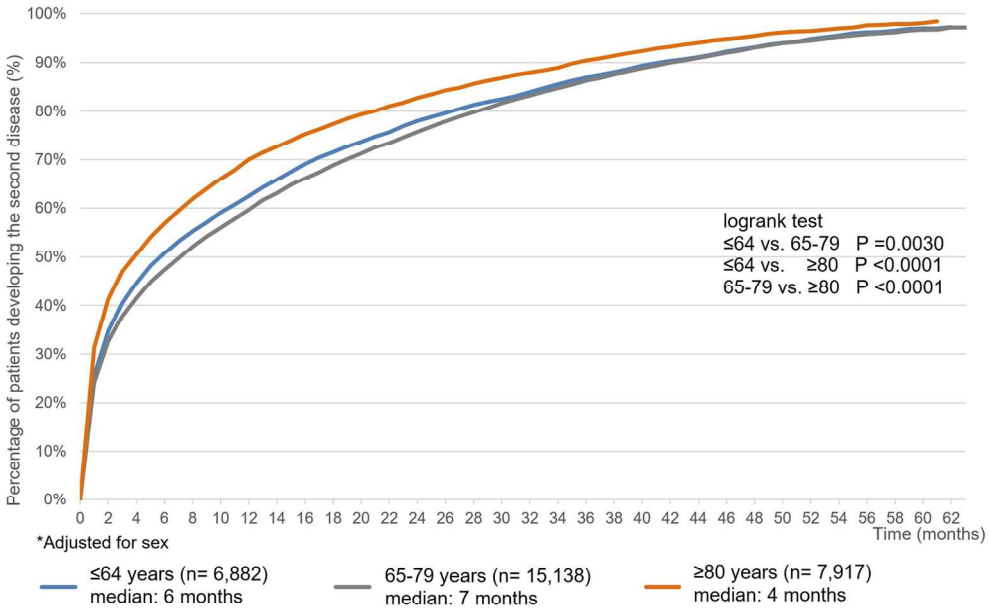


Fig. 8 Time delay until the development of HF after AF in different age groups

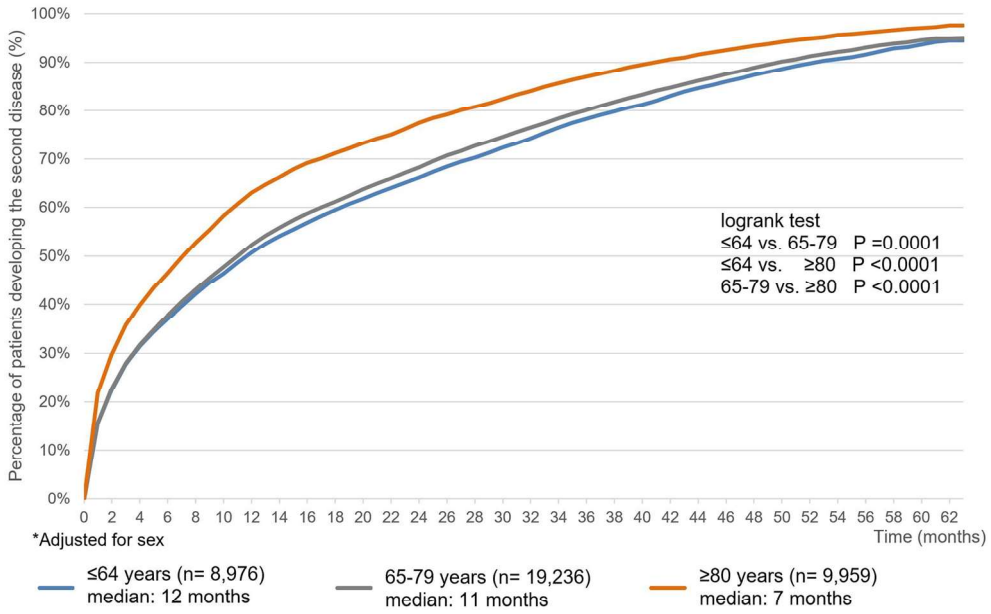


Fig. 9 Time delay until the development of AF after HF in different age groups

according to the sequence of AF and HF. Simultaneous presentation was associated with the lowest survival curve with early separation after 3 months. Curves related to the AF versus HF first sequences separated after 6 months indicating significantly better survival at a 5% difference in relative risk (RR) when HF followed AF, thereby confirming the findings in previous reports [16–18], including the recently published data from the Danish study [15].

To our knowledge, our study is the first one which analyzed mortality in different sequences in different age groups. The lowest survival was consistently demonstrated in simultaneously diagnosed patients in all age groups studied. In the 65–79-year range (Fig. 3b), which contained the largest cohort within the study, mortality rates in the different sequences followed the same pattern as in the whole cohort. In patients below 65 (Fig. 3a), representing the age group smallest in size, survival advantage of the AF → HF sequence was even larger as compared to the HF → AF and the simultaneous sequences (relative risk reduction [RRR] = 25% and 29%, respectively). As expected, better survival rates were detected in this youngest cohort with any sequence, thereby median values could not be calculated with 66 months follow-up. Strikingly low survival rates (4–7 months) were demonstrated in patients above age 80 with all scenarios (Fig. 3c). Furthermore, mortality rates with the AF → HF versus HF → AF sequences reversed in this age group: patients had better survival when AF presented in a previously diagnosed HF condition. However, differences with small absolute values mitigate the clinical relevance of the statistical significance of this comparison.

Table 2 Timing scenarios of AF and HF presentation in different studies

Occurrences of the different timing scenarios (%)			
Study	**AF → HF**	**HF → AF**	**Simultaneous**
Our study	27	35	37.5
Pallisgaard et al. [15]	40	27	33
Wang et al. [16]	38	41	21
Smit et al. [17]	75*	25	N/A
Chamberlain et al. [18]	59	41	N/A

AF atrial fibrillation, *HF* heart failure

*AF → HF or simultaneous, *N/A* not available

Importantly, the endpoint of our study was all-cause mortality. Types of mortality (cardiovascular versus non-cardiovascular etc.) could not be captured from the database. Accordingly, some of the deaths in our cohort may not have related to either AF or HF.

We also analyzed mortality differences related to gender in the different timing scenarios and age groups. For the total patient population, better survivals were demonstrated in women with all three sequences. However, no sex difference in survival was demonstrated above age 80 with any patterns. The lack of survival benefit of female sex above 80 years is not surprising considering the dramatically low overall survival in this age group (Figs. 4, 5, 6).

Comparing data from the Danish [15] and the Hungarian databases, higher mortality rates were found in our patients at 1 year with both the AF→HF (35 vs. 25%) and the HF→AF (37% vs. 30%) sequences (Table 3). These differences became smaller at 3 years with these two sequences. However, dramatically lower survivals were detected in simultaneously diagnosed cases in our study at both follow-up timepoints.

We cannot provide a definite explanation for this difference between the results of two large-volume, nationwide European studies with many similarities in design. Although simultaneously diagnosed patients represented the oldest cohort in our, while the youngest one in Pallisgaard's study, the mean and median ages (74.63 and 75 years) in the two cohorts were still comparable. However, life expectancies at birth in Denmark versus in Hungary were 79.4 versus 70.69 years for male patients and 83.1 versus 77.52 years for female patients, and mortality rates/1000 inhabitants were 9.84 versus 14.5, respectively (data from 2021) indicating significant differences in the general health status of the two populations. Although details of comorbidities in the two studies might have suggested at least a partial explanation for the differences, these data were not captured in our trial. The low median survival detected in our patients suggest that many of these individuals were probably latecomers, who were seeking medical help at an already advanced stage of their disease.

Table 3 Mortality in the Hungarian and in the Danish studies according to the sequence of AF and HF

Study	AF→HF	HF→AF	Simultaneous
1-year mortality (%)			
Hungarian**	35	37	45
Danish***	25	30	20
3-year mortality (%)			
Hungarian**	46	49	58
Danish***	42	50	35
Hazard ratio of mortality			
Hungarian**	0.84	0.88	1.0
Danish***	1.08	1.26	1.0

AF atrial fibrillation, *HF* heart failure

*Hazard ratios of mortality are displayed in comparison with mortality in the simultaneous cohorts

**Papp T et al., All-cause mortality of AF and HF in the same patient: does the order matter?

***Pallisgaard J et al., Atrial fibrillation onset before heart failure or vice versa: what is worst? (Reference no. [15])

HF after AF was diagnosed after a shorter delay (median 6 months) than vice versa (median 10 months) in the whole patient population (Fig. 7). These time delays demonstrated slight changes with increasing age in both sequences (Figs. 8, 9). However, consistently shorter time delays were detected between the two comorbidities with the AF→HF scenario across all age groups.

The differences in both the time delays and in life expectancies demonstrated in our study may be related to the different underlying patomechanisms of the two scenarios. In the case when HF occurs first, the leading cause of developing AF is likely to be related to electromechanical remodeling, which starts later during disease progression, but indicates a more advanced stage of HF which is less likely to respond to therapy. In contrast, HF may develop earlier after AF as a result of tachycardia-induced left ventricular cardiomyopathy, the loss of atrial pump function, and the irregularity of the ventricular cycle lengths [19]. Patients with the latter scenario might respond better to evidence-based

HF and antiarrhythmic therapy, especially when it is initiated early in the course of the disease. Arrhythmia-induced left ventricular dysfunction, referred to as tachycardiomyopathy may improve even with therapy targeting only the arrhythmia (rhythm or rate control) with partial or even full resolution of LV dysfunction. Furthermore, data from the CASTLE-AF Trial [20], and a few single-center studies [21] demonstrated that the restoration of sinus rhythm with left atrial ablation in HF patients may result in reverse remodeling of the LV and a reduction in all-cause mortality. Whether the order AF and HF present may modify the favorable effect of catheter ablation in these patients remains to be clarified.

Clinical Implications

Among other studies including patients with concomitant AF and HF, our study enrolled the largest number of patients. We confirmed previous findings in the literature in that the sequence of presentation of these conditions in the same patient have significant prognostic implications. Furthermore, the survival benefit with the AF→HF sequence is larger at younger age, while the differences in magnitude are shrinking with age, especially above 80 years. The survival advantage of female sex also disappears in the oldest cohort. These observations suggest that family physicians, internists or cardiologists should pay attention to the sequence these conditions present. Newly discovered AF in a stable patient with HF should be considered as a "red flag" of possibly rapid deterioration. The closer monitoring and early intensification of available therapy to the maximum level is justified involving heart failure and arrhythmia specialists in these cases. Although recent developments in the pharmacotherapy for HF including the novel classes of angiotensin receptor-neprilysin inhibitor (ARNI) and sodium-glucose cotransporter-2 (SGLT2) inhibitors are based on the results of large-scale multicenter trials, no results are available on those patients who had coexisting AF and HF with different orders of presentation. Evaluating the array of therapeutic options in this specific cohort should therefore be an important consideration while planning future studies. In addition, the sequence AF and HF present should be considered while assessing the benefit of pharmacotherapy and catheter ablation strategies.

Limitations and Strength

This is a longitudinal database study which included more than 100,000 patients. Major limitations of our investigation are that no data were collected on comorbidities and on treatment of these patients. Study participants were identified by ICD codes with no details on the types of AF and HF and the exact cause of death remained unknown. Novel HF medication options like ARNI and SGLT-2 inhibitors were not available during the study period. However, the large number of patients, including in- and outpatients collected from a database covering the whole Hungarian population, and the more than 5-year follow-up adds strength and significance to our findings.

CONCLUSIONS

This nationwide study including more than 100,000 patients with coexisting AF and HF demonstrated that the order the two conditions present have significant prognostic implications. Patients with AF presenting after HF, and those diagnosed simultaneously with the two conditions have 8 and 25 months shorter survival, respectively, as compared to patients with the AF→HF sequence. These differences are shrinking in magnitude with age, as median survivals are below 7 months with any sequence in the age cohort above 80 years. Male patients have worse prognosis as compared to women, except in the oldest age group. These observations suggest that physicians should pay attention to the order these conditions present while treating these complex cases.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. György Rokszin is employed by the company RxTarget Ltd. His contribution to this study analysis was financially compensated by the Hungarian Society of Cardiology. Béla Merkely reports grants or contracts from Medtronic and Boston Scientific, and personal fees from Biotronik and Abbott. Zoltán Járai reports payment or honoraria from Bayer, Boehringer, Pfizer, Richter Gedeon, Egis, Krka, Berlin Chemie – Menarini, Novo Nordisk, support for attending meetings from Egis, advisory board membership at Novo Nordisk, and board membership at the European Society of Hypertension, Hungarian Society of Hypertension, Hungarian Society of Cardiology. Tímea Papp, Zoltán Kiss, Dávid Becker, Andrási Jánosi and Zoltán Csanádi declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval. Anonymized data provided by the National Health Insurance Fund for this research did not contain any personal information which could be used to identify the patients. The study protocol was reviewed and confirmed by the National Health Insurance Fund (identification number: I043/125/2021) and they provided us the anonymized database which was later used for statistical analysis.

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