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Population studies in atrial fibrillation patients based on the National Health Insurance Fund database

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The PhD Defense takes place at the Auguszta Lecture hall of the University of Debrecen, Faculty of Medicine at 2 P.M. on 11th of December, 2024.

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1 List of abbreviations

AF – atrial fibrillation

ARNI – angiotensin receptor-neprilysin inhibitor

CHA_2DS_2-VASc – C – congestive heart failure, H – hypertension, A_2 – age, D – diabetes mellitus, S_2 – stroke, V – vascular disease, A – age, Sc – sex category

CI – confidence interval

COViD-19 – coronavirus disease 2019

DOAC – direct oral anticoagulant

HAS-BLED – H – hypertension, A – abnormal liver/renal function, S – stroke, B – bleeding in the histrory, L – labile INR, E – elderly, D – drug or alcohol abuse

HF – heart failure

HR – hazard ratio

ICD – International Classification of Diseases

INR – International Normalized Ratio

NHIF – National Health Insurance Fund

OAC – oral anticoagulant

RR – relative risk

RRR – relative risk reduction

SGLT2 - sodium-glucose cotransporter-2

TIA – transient ischemic attack

TTR – time spent in therapeutic range

VKA – vitamin K antagonist

2 Introduction

2.1 Definition and epidemiology of atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia, characterized by supraventricular origin, uncoordinated atrial activation and ineffective left ventricular contraction. AF has an estimated prevalence of 3% in the general population worldwide and between 2,37% and 2,67% in Hungary. The incidence and prevalence of AF displays a constantly rising tendency. Due to a set of comorbidities and the significantly increased mortality AF poses an enormous health care burden.

2.2 Factors influencing prognosis in atrial fibrillation

It is well known that patients with AF are more prone to developing thromboembolic complications such as ischemic stroke, leading to a higher mortality risk, which could be significantly reduced by anticoagulation. The presence of AF increases the risk of mortality by two-fold and the risk of stroke by 2.4-fold. The most popular score in the assessment of stroke risk of AF patients is the CHA_2DS_2-VA, giving points for C – congestive heart failure (1 point), H – hypertension (1 point), A_2 – age ≥75 years (2 points), D – diabetes mellitus (1 point), S_2 – previous stroke or transient ischemic attack (TIA) (2 points), V – peripheral vascular disease, A – age between 65-74 years (1 point). Initiation of oral anticoagulant (OAC) therapy is recommended in the presence of at least two of the mentioned comorbidities and should be considered if only one risk factor is present. At OAC therapy initiation the bleeding risk of patients should also be assessed. The most commonly used score is the HAS-BLED, giving points for H – hypertension (1 point), A – abnormal liver and renal function (1-1 points), S – stroke (1 point), B – bleeding in the history of the patient (1 point), L – labile INR (International Normalized Ratio) levels (1 point), E – elderly, age ≥65 years (1 point), D – drug or alcohol abuse (1-1 points).

The prognosis of AF patients is largely determined by the presence of heart failure (HF), which is considered a thromboembolic risk factor and is part of the CHA_2DS_2-VA score.

2.3 Atrial fibrillation and stroke prophylaxis

Although vitamin K antagonists (VKAs) have been widely used for stroke prophylaxis in AF, direct oral anticoagulants (DOACs) are recommended based on the guidelines, considering the several shortcomings of VKA therapy. These include the frequent need for INR monitoring

and dose adjustments, and numerous food and drug interactions. In addition, Azoulay et al suggested that patients treated with VKAs may be at an increased risk of thromboembolism during the first 30 days of treatment, not only because of the delay in reaching therapeutic INR levels, but also as a result of an increased prothrombotic activity attributed to the early depletion of protein C due to its short half-life early after the initiation of VKA treatment. Real-world registries confirmed the benefit of DOACs compared with VKA, similarly to what was shown in the randomized clinical trials.

2.4 Atrial fibrillation and heart failure

AF and HF are growing cardiovascular epidemics frequently encountered in the same patient. The prevalence of HF has an estimated prevalence of 1-2% in the adult population. However the incidence of HF seems to be declining in developed countries, the prevalence is going to rise because of the ageing population and the increased life expectancy at birth. The 5-year survival of HF patients have doubled between 1970 and 2000 mainly due to the improvements in the diagnosis and treatment of patients. However, the overall mortality rate is still high in this population, representing a global economic burden, as it was highlighted by Cook et al.

AF and HF often coexist due to the common elements of the pathomechanism they share. AF leads to the development of HF mainly by the increased heart rate, irregularity and the loss of atrial systole. Sustained tachycardia results in tachycardia-induced cardiomyopathy with the failure and dilation of the left ventricle. A temporary tachycardia-induced increase in the responsiveness of myofilaments to calcium is followed by downregulation and cell apoptosis. The short R-R intervals secondary to the high heart rate lead to impaired left ventricular relaxation and negative hemodynamic consequences. The loss of atrial systole escalate the diastolic dysfunction and heart failure symptoms. After all, HF is reversible in the early stage of AF. HF precipitates the development of AF through atrial stretch, fibrosis and a set of neurohormonal changes. Left ventricular failure leads to increased left atrial pressure and left atrial enlargement, with a consequently higher AF burden. Beside structural changes, the levels of B-type natriuretic peptids will increase as a result of the left ventricular failure. A proinflammatory state occurs with sympathetic nervous system and renin-angiotensin-aldosterone system activation.

The coexistence of AF and HF increases mortality risk regardless of the ejection fraction of patients. 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. However, no relevance of the AF-HF sequence was demonstrated in the COMET and PRIME II trials. 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. These observations have also been confrmed by recently published data from a nationwide Danish database based on more than 49 000 patients with the diagnosis of both AF and HF: signifcantly better survival was demonstrated when AF was diagnosed before HF than vice versa.

2.5 Hungarian data on atrial fibrillation and heart failure

AF and HF are prevalent diseases associated with significant cardiovascular mortality and morbidity. Big data analysis may provide important information on the course of the diseases, taking into consideration that only a few hungarian publications are available in this subject. Tomcsányi et al in a database study estimated a total of three hundred thousand AF patients in Hungary. Simonyi et al in a study based on the data provided by the National Health Insurance Fund (NHIF) assessed the persistence of Hungarian AF patients on DOAC vs. VKA therapy. Data on HF patients were published based on the National Heart Failure Registry. However, only a small number of subjects were enrolled with the participation of a few centers from our country, therefore the results were not representative.

3 Aims

Our aim was to provide representative data on Hungarian atrial fibrillation and heart failure patients based on the database of the National Health Insurance Fund focusing on the following subjects:

1. We assessed the mortality risk of atrial fibrillation patients on different types of oral anticoagulants, with a particular attention to the early treatment period.
2. We analyzed the occurrence of various sequences in which atrial fibrillation and heart failure present, the time delays between the two conditions and all-cause mortality associated with different scenarios.

4 Patients and methods

4.1 Anticoagulant therapy of atrial fibrillation patients

4.1.1 Characteristics of patients receiving different types of oral anticoagulants

This nationwide, retrospective, longitudinal study included patients with AF from January 1, 2011, through December 31, 2016, using the NHIF database. Because Hungary has a single, state-owned insurance company, the NHIF database contains data on in- hospital, outpatient, and prescription activities of almost 100% of the Hungarian population. International Classification of Diseases (ICD), Tenth Revision was used to select patients with AF from the database. To verify patients newly diagnosed with AF during the study period (2011–2016), a 2-year screening was also performed through the previous years (2009-2010). Patients with at least 2 occurrences of ICD code I48 (AF diagnosis) within a period of 30 to 365 days, related to in-hospital, outpatient, or prescribing activities, with a prescription of VKA or DOAC therapy for AF diagnosis were included in the analysis. DOAC medications available in Hungary during this period included dabigatran, rivaroxaban, and apixaban. Patients with only one occurrence of the I48 ICD code who died within 60 days of disease onset were also included in the analysis if they had at least one VKA or DOAC prescription. The index date of diagnosis was defined as the date of the first ICD I48 record. Patients with valvular AF (mechanical heart valves, severe mitral stenosis; ICD-10 codes I05 and I3420), those who died in the first 14 days after AF diagnosis, or who were aged <30 years were excluded from this analysis. The dates of death were retrieved from the NHIF database. Stroke as a prior event was defined as at least 2 occurrences of a primary or a secondary discharge ICD-10 code of stroke (I61, I6290, I63, I64, and I74) in outpatient or inpatient records before AF diagnosis. Data on INR are not available in the NHIF database and therefore were not used in the assessment of bleeding risk. Antiplatelet treatment was defined as the prescription of either aspirin or another platelet aggregation inhibitor (ie, clopidogrel, ticagrelor, prasugrel) treatment. Parameters were used to calculate thromboembolic risk according to the CHA_2DS_2 -VASc score. For the assessment of bleeding risk, the elements of the HAS-BLED score were collected except for “Labile INR,” as those parameters were not available in the database; the term bleeding risk is therefore used consistently throughout the article. The overall effect of VKA versus DOAC as the initial therapy on mortality was calculated from the diagnosis of AF until the end point event (death) occurred or until the end of follow-up. Patients were followed up until the end of the study period (October 31, 2017) or up to 36 months of treatment. The relative risk of mortality was

also calculated separately for different follow-up durations after the initiation of OAC therapy: 0- to 3-month, 4- to 6-month, 7- to 12-month, and 13- to 24-month time frames. Furthermore, outcomes were calculated according to age, sex, CHA_2DS_2-VASc score, and bleeding risk. The following age groups were created for analysis: 30 to 59 years, 60 to 79 years, and ≥80 years. The study protocol was reviewed and confirmed by the NHIF (identification number: S04/161/2016).

4.1.2 Statistical analysis of patients receiving different types of oral anticoagulants

Baseline statistics were determined for both therapy arms. The 3-year survival rates were plotted on Kaplan- Meier curves, and hazard ratios (HRs) were determined by using Cox regression. For the total population and comorbidities, we adjusted for age and sex; in the other cases, adjustment was made only for sex. Survival and relative risk reduction (RRR) were also calculated for different time points of follow-up, including 0 to 3 months, 4 to 6 months, 6 to 12 months, and 13 to 24 months. To calculate the relative risk (RR), we determined the number of deaths during the examined period (event number), the sum of patients still living in the last month of the period, and the number of patients who died during the period. The direct standardization method was applied on the data, in which the standard population was created uniting the therapy arms. Results were considered significant at $P<0.05$. The analysis was performed by using R version 3.6.1.

4.2 The analysis of patients with coexisting atrial fibrillation and heart failure

4.2.1 Characteristics of patients diagnosed with both atrial fibrillation and heart failure

We searched the database of the 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 fnancial reimbursement, health care providers need to enter the code of the primary diagnosis a patient was treated for using the 10th review of ICDs. 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. Anonymized data provided by the NHIF for this research did not contain any personal information which could be used to identify the patients. The study protocol was reviewed and confrmed by the NHIF (identifcation number: I043/125/2021) and they provided us the anonymized database which was later used for statistical analysis.

4.2.2 Data analysis and study periods of patients with coexisting atrial fibrillation and heart failure

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 frst diagnosis of AF, or AF presented after the frst 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 signifcant 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.

4.2.3 Statistical analysis of patient population with coexisting atrial fibrillation and heart failure

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

5 Results

5.1 Results from the analysis of patients receiving different types of oral anticoagulants in atrial fibrillation

5.1.1 Baseline characteristics of patients on different types of anticoagulants

Between January 1, 2011, and December 31, 2016, a total of 144 394 patients with AF meeting the study inclusion criteria were identified. Overall, 49.89% of the studied population was male, and the mean (SD) age was 71.8 (10.75) years. During this period, 14 469 patients with AF were initiated on DOAC treatment and 129 925 patients started on VKA therapy for thromboembolic prophylaxis. The mean age of the AF population in the DOAC arm was 73.5 (11.31) years, the mean CHA_2DS_2-VASc score was 4, and the mean bleeding risk score was 3.2 (1.2); these characteristics in the VKA arm were 71.7 (10.67) years, 3.7 (1.7), and 3 (1.16), respectively ($P<0.0001$). The proportion of patients with associated heart failure was 13.19% in the DOAC arm and 12.93% in the VKA arm ($P=0.377$). The occurrence of a prior stroke was slightly higher in the DOAC arm (19.85% vs 13.02%; $P<0.0001$).

5.1.2 36 months' survival with different types of oral anticoagulants

The likelihood of survival at 36 months was 77.31% with VKA and 80.78% with DOAC treatment, which corresponds to a 28% improvement in the 3-year survival on DOAC, adjusted by regression during the follow-up (hazard ratio [HR]=0.72; 95% CI, 0.69–0.75; $P<0.001$).

There was no clinically relevant difference in the 3-year survival benefits of DOAC therapy between female and male patients (HR for male patients, 0.72 [95% CI, 0.670.77; P<0.001]; HR for female patients, 0.72 [95% CI, 0.67–0.77; P<0.001]). The overall mortality benefit with a DOAC was also consistent across other subgroups of age, initial risk for thromboembolism, and bleeding; however, the relative benefit was even more apparent in some subsets of patients. Importantly, younger (aged 30–59 years) patients with AF initiated on DOAC therapy had the greatest RRR (53%) in mortality compared with VKA therapy; nonetheless, the benefit was still significant in the octogenarian cohort (RRR, 20%).

DOAC treatment also yielded a benefit of greater magnitude in the lower CHA_2DS_2-VASc score segments: the HR was 0.55 (95% CI, 0.40–0.77; P=0.001) in the 0 to 1 score range, whereas this benefit decreased to 21% when the CHA_2DS_2-VASc score was ≥7 at the time of AF diagnosis. Similarly, lower bleeding risk was also associated with a more marked benefit of DOAC therapy (RRR, 50%) than in patients with ≥4 risk factors (RRR, 22%).

5.1.3 Mortality risk at different points of the follow-up

When the mortality risks in the 2 treatment arms were compared at different time points of the follow- up period, the most significant relative benefit was found in the first 3 months after the AF diagnosis. The overall RRR of all-cause mortality in the DOAC arm was 33% in the first 3 months, and 6% in the second year. These time-dependent differences were more obvious in female patients (RRR, 41% at 3 months and 5% throughout the second year) than in male patients (RRR, 31% and 7%, respectively).

Mortality risks at different time points of the follow- up period were also analyzed in the various age groups. The largest difference in RRR in relation to treatment duration was observed in the 30- to 59-year-old age group with an RRR of 68% (95% CI, 0.220.45; P<0.001) in the first 3 months, and a RRR of 34% (95% CI, 0.51–0.86; P=0.002) between 4 and 6 months. Similar trends with smaller differences in RRR at different time points of follow-up were observed in the older age groups.

5.2 Results from the analysis of patients with coexisting atrial fibrillation and heart failure

5.2.1 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 signifcantly higher in the simultaneous group (P<0.0001).

5.2.2 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 HRs (95% CI of 0.95 (0.93–0.97) and 0.84 (0.82–0.85), respectively (P<0.0001) compared to the HF→AF sequence.

The Kaplan–Meier analysis of different age subgroups was also performed. In the less than 65-year-old age cohort the mortality of AF→HF group was signifcantly 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). In the 65–79-year-old age group the survival of the AF→HF group was 63 months, significantly 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), 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); 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.

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 RRR 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). 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).

5.2.3 The delay between the diagnoses of atrial fibrillation and heart failure

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

6 Discussion

6.1 Questions raised by the analysis of different types of oral anticoagulants in atrial fibrillation

A meta-analysis of the 4 pivotal clinical trials comparing warfarin with all DOAC drugs currently available for the treatment of patients with nonvalvular AF found a 10% reduction of mortality with DOAC therapy. We analyzed the data of more than 140 000 patients from the Hungarian insurance database and found a significant 28% reduction in all-cause mortality with DOACs. These results are similar to the 33% RRR reported in a meta-analysis of 21 Asian registries. The mortality of patients on VKA therapy is largely depending on the time spent in therapeutic range (TTR). However, no mortality benefit was found with DOAC treatment in an analysis by Själander et al that included patients with TTR>70% on warfarin therapy. These differences regarding the relative benefit of DOACs over VKA are largely related to the

diversity in the quality of warfarin therapy: poor patient compliance as reflected by suboptimal TTR values is associated with a more marked advantage with DOACs compared with warfarin. TTRs reported in randomized trials are known to be higher than those measured in community practice: a meta-analysis found a 66.4% mean TTR in randomized trials while only 56.7% in registries. Wide variations in TTR values are depending not only on patient characteristics but also on geographical regions. Indeed, the optimal value of TTR≥70% is difficult to achieve in clinical practice. Cotté et al reported an average TTR range between 65.3% and 72.6% in Western European countries, with the 70% cutoff met only in the United Kingdom. Moreover, in a study covering a larger geographical area, including 45 countries, Singer et al reported an even more pronounced regional variability of TTR, with an average value of only 50% in Eastern Europe. TTR is also influenced by age, body mass index, concomitant medications, and genetic factors.

In a study based on the prescription database of the Hungarian NHIF, the 1-year persistence with VKA versus with DOACs was reported at 53.9% and 72.6%, respectively, and a difference of even greater magnitude was found in those naive to OAC therapy (39% and 65.7%). A better persistence at 1 year with DOACs compared with VKA was also shown in an analysis from the GLORIA-AF registry.

Of note, the baseline thromboembolic risk in our Hungarian patient cohort was higher (4 [1.78] on DOACs and 3.7 [1.7] on VKAs) compared with this risk in most real-world data or in the Phase III studies. Nonetheless, our mortality data also confirm the superiority of DOAC treatment for nonvalvular AF in this high-risk population, an observation relevant to many geographical regions with similar attitude and pattern of thromboembolic prophylaxis worldwide.

The overall mortality benefit with a DOAC was consistent in our study across different subgroups of age, sex, initial risk for both thromboembolism, and bleeding. Surprisingly, an even more marked relative risk reduction was observed in younger patients and in those with lower CHA_2DS_2-VASc-scores, representing a more favorable thromboembolic and bleeding risk profile. A plausible explanation for this finding may be that younger patients with fewer comorbidities are less aware of their health problems, which influences their adherence to the prescribed anticoagulant medication, particularly to VKA therapy. Singer et al reported a TTR at 33.3% among patients with a CHA_2DS_2-VASc score of 1, supporting the concept that the excess mortality of the patients undergoing anticoagulation with VKA is likely related to inadequate compliance. Importantly, a meta-analysis of the 4 randomized DOAC trials found

that cardiac death (heart failure, sudden cardiac death, and myocardial infarction altogether) accounted for 46% of total mortality, whereas thromboembolic or bleeding- related fatal events were found at a surprisingly low rate each of <6%. These numbers were calculated, however, for the whole study groups of these trials; anticoagulation-related events (thromboembolism and bleeding) likely have a more significant contribution to total mortality in younger patients with fewer comorbidities.

In addition to the long-term comparison, we also evaluated the short-term mortality with DOACs versus VKA therapy as higher complication rates including death have been reported within the first 30 days after initiation of VKA therapy, a phenomenon also referred to as the "VKA stress test." Difficulties faced by the patients and the treating physicians during the initiation and the early phase of VKA therapy include dose optimization, diet restrictions, and the need for regular and frequent monitoring of the INR. A time-dependent difference was also evident in a database study performed in the United Kingdom, as TTR at the first INR measurement was only 40%, which then rose to 60% by the tenth measurement. Furthermore, better compliance with DOACs throughout the early phase of OAC therapy was also suggested by the 1-year follow-up results of the GLORIA-AF registry, as drug persistence with DOACs was better at the beginning of treatment compared with that of VKA therapy. In addition to the compliance issues and the difficulties obtaining a therapeutic INR level, the early prothrombotic activity of VKAs has to be considered as a potential explanation for the higher complication rates at therapy initiation. The additional risk involved with all these mechanisms can be mitigated with the use of DOACs, which might explain why the success and the safety of this therapy are less sensitive to patient cooperation than anticoagulation initiation with VKA. Our data support this theory, as we found a substantially higher relative risk of all-cause mortality with VKAs compared with DOACs in the early phase after AF diagnosis than in later treatment periods. In addition, the increased benefit of DOAC treatment early after therapy initiation was even more pronounced in patients aged <60 years, also in support of the compliance problems in younger patients. Indeed, the relative difference in the short- versus the long-term benefit of DOACs was greater in our study than what has been reported in the few available studies.

The current study revealed no significant sex-related differences during long-term follow-up: male patients, similarly to female patients, had a 28% better survival rate at 3 years with DOAC therapy. However, in the first 6 months after initiation of anticoagulant treatment, female patients had significantly higher survival rates with DOAC therapy compared with male patients.

Female sex by itself is a known risk factor for stroke and consequently for a higher all-cause mortality in case of AF. In older patients the higher thromboembolic risk is related to menopause, while in younger patients high hormone levels (hormone therapy, oral contraceptives, etc.) increase the risk.

6.1.1 Clinical implications

In this large nationwide retrospective database study, we showed that DOAC treatment of patients with nonvalvular AF is associated with an overall mortality risk reduction across different groups of sex, age, and thromboembolic and bleeding risk. DOACs yielded a significantly better survival during the early phase of the therapy and were efficient on long-term follow-up as well. More pronounced RRR was observed in the early period after the diagnosis of AF, in the younger age cohort, in female patients, and in those with lower initial thromboembolic and bleeding risk.

6.1.2 Limitations

As a limitation, this study included patients having had at least 2 recorded visits, whereas data from patients with silent AF and nonadherent patients were not recorded. Furthermore, due to the retrospective nature of our study, we were not able to calculate TTR because laboratory test results were not available in the database. The use of ICD codes as proxies for AF diagnosis and the presence of other medical conditions represent major limitations. Similarly, the exact cause of mortality and comorbidities could not be determined. To assess the risk of thromboembolism and bleeding in the 2 groups, we calculated the CHA_2DS_2-VASc and bleeding risk scores. Although propensity matching was not performed, these scores indicated that patients on DOAC had higher risk for both thromboembolism and for bleeding. Therefore, favorable outcome results found with DOACs were shown despite less favorable baseline characteristics. In our registry, DOACs were underused compared with VKAs during the study period (2011–2016) as reimbursement for DOAC therapy by health insurance has been available in Hungary since May 2014, and relatively few patients could afford the therapy before that time.

6.2 Questions raised by the analysis of patients with coexisting atrial fibrillation and heart failure

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.

Similarly to the Framingham study, in our analysis the HF→AF scenario was more common and the prognosis was less favorable compared to the AF→HF sequence. Smit et al in a prospective study analyzed the data of AF patients with new onset or previously diagnosed HF. Although the best prognosis was associated with the AF→HF sequence, this represented the most frequent scenario in their study. Chamberlain et al in a study including HF patients with new onset or previously diagnosed AF demonstrated similar results. In a recently published data from a Danish database study very similar in design to our analysis, a better prognosis was associated with the AF→HF sequence.

To our knowledge, our study is the frst 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. 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.

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 signifcance of this comparison. Importantly, the endpoint of our study was allcause 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.

Comparing data from the Danish 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. 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.

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

6.2.1 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. Patients with this scenario might respond better to evidence-based HF and antiarrhythmic therapy, especially when it is initiated early in the course of the disease. Based on the results of CASTLE-AF trial with the restoration of sinus rhythm by catheter ablation, a concomitant reduction in hospitalization for heart failure and improvement in mortality can be achieved. Moreover, Reant et al demonstrated left atrial and left ventricular reverse remodeling with

improvement in left ventricular function following catheter ablation in patients suffering from both AF and HF.

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 fag” 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, only a few results are available on those patients who had coexisting AF and HF with different orders of presentation. Mauriello et al in a review refers to oxidative stress as a key factor in the patomechanism of both AF and HF. Novel HF therapies effectively reduce oxidative stress, therefore have a potentially beneficial effect on the appearance and recurrence of AF as well. ARNI therapy and SGLT2 inhibitors have positive effects also by improving haemodynamics and consequently reducing left atrial stretch. These findings were confirmed by a few retrospective and prospective studies including a small number of patients. 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. The simultaneously diagnosed AF and HF cohort is represented by latecomers, with advanced stages of the diseases, reflecting the motivation of East-Central-European patients to seek medical advice.

6.2.2 Limitations of our study

A major limitation of our investigation is 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.

6.3 New scientific observations

- In a large nationwide study we confirmed that direct oral anticoagulant treatment of patients with nonvalvular atrial fibrillation is associated with an overall mortality risk reduction compared to vitamin K antagonist therapy.
- We were the first to demonstrate in real-world settings the survival benefit of direct oral anticoagulants vs. vitamin K antagonists during the first months of the therapy.
- We showed that direct oral antagonists can significantly reduce mortality risk in female patients and in the younger age cohort compared to vitamin K antagonist therapy.
- In a large sample size study including patient with coexisting atrial fibrillation and heart failure we showed that the order the two conditions present have significant prognostic implications.
- In our study the least common scenario was heart failure presenting following atrial fibrillation, and most commonly atrial fibrillation and heart failure were diagnosed at the same time.
- We demonstrated that in patients with preexisting atrial fibrillation heart failure develops with a shorter delay and the prognosis is favorable.
- We showed that in patients with preexisting heart failure atrial fibrillation develops with a longer delay and the prognosis is poor.

7 Summary

Background: The constantly rising incidence and prevalence of atrial fibrillation (AF) poses an enormous healthcare burden. Anticoagulation in AF is essential, considering the increased risk of thromboembolism and mortality in these patients. AF is often associated with heart failure (HF) due to the common comorbidities and elements of the pathomechanism they share. Limited Hungarian data exist regarding the survival of patients treated with different types of oral anticoagulants. The potential significance of the order of presentation of AF and HF in the same patient is also unknown. Therefore, our **aim** was to provide representative Hungarian data on these two entities.

Methods 1: The National Health Insurance Fund (NHIF) database was searched to identify patients treated with vitamin K antagonist (VKA) or direct oral anticoagulant (DOAC) as a thromboembolic prophylaxis for AF between January 1,2011 and December 31, 2016.

Results 1: A total of 144 394 patients with AF treated with either a VKA (n = 129 925) or a DOAC (n = 14 469) were enrolled. A 28% improvement in 3-year survival with DOAC treatment compared with VKA treatment was shown. The mortality risk reduction with DOACs was 39% within the first 3 months, and 13% in the second year of the therapy. Mortality reduction with DOACs was consistent across different subgroups. However, younger patients (30-59 years old) initiated on DOAC therapy had the greatest risk reduction (HR = 0,47; 95% CI, 0,35-0,62, P<0,001) in mortality. Furthermore, DOAC treatment also yielded a benefit of greater magnitude in those with fewer thromboembolic (0-1 CHA_2DS_2-VASc score segment, HR = 0,51; 95% CI, 0,35-0,75, P=0,001) and bleeding risk factors (0-1 score segment, HR = 0,49; 95% CI, 0,33-0,75, P=0,001), and in female patients at the beginning of therapy (HR = 0,57; 95% CI, 0,52-0,62, P<0,001).

Conclusions 1: Thromboembolic prophylaxis with DOACs yielded significantly lower mortality compared with VKA treatment accross different subgroups of nonvalvular AF patients. The largest benefit was shown in the early period after treatment initiation, as well as in younger patients, in female, and in those with fewer thromboembolic and bleeding risk factors.

Methods 2: Patients diagnosed with both AF and HF between January 1, 2015 and December 31, 2021 were enrolled from the 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 2: 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 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 2: We confirmed that the sequence of presentation of AF and HF in the same patient have significant prognostic implications. In our study the most common timing scenario was the simultaneous presentation of AF and HF, while the least frequent was the development of HF after AF. In AF patients HF appeared earlier and was associated with a lower mortality. In HF patients AF developed later during the course of the disease, indicating a poor prognosis. Patients diagnosed simultaneously had the wors prognosis.

8 List of publications

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Registry number: DEENK/478/2024.PL
Subject: PhD Publication List

Candidate: Tímea Bianka Papp
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Papp, T. B.**, Rokszin, G., Kiss, Z., Becker, D., Merkely, B., Járai, Z., Jánosi, A., Csanádi, Z.: All-Cause Mortality of Atrial Fibrillation and Heart Failure in the Same Patient: Does the Order Matter?
   Cardiol. Ther. 13 (3), 615-630, 2024.
   DOI: http://dx.doi.org/10.1007/s40119-024-00378-1
   IF: 3 (2023)
2. **Papp, T. B.**, Kiss, Z., Rokszin, G., Fábián, I., Márk, L., Bagoly, Z., Becker, D., Merkely, B., Aradi, D., Dézsi, C. A., Járai, Z., Csanádi, Z.: Mortality on DOACs Versus on Vitamin K Antagonists in Atrial Fibrillation: Analysis of the Hungarian Health Insurance Fund Database.
   Clin. Ther. 45 (4), 333-346, 2023.
   DOI: http://dx.doi.org/10.1016/j.clinthera.2023.03.008
   IF: 3.2

List of other publications

3. Nagy, L. T., **Papp, T. B.**, Urbancsek, R., Jenei, C., Csanádi, Z.: Right Superior Pulmonary Vein Parameter Determined by Three-Dimensional Transesophageal Echocardiography is an Independent Predictor of the Outcome After Cryoballoon Isolation of The Pulmonary Veins.
   Cardiol. J. 30 (6), 1010-1017, 2023.
   DOI: http://dx.doi.org/10.5603/cj.95381
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4. Nagy, L. T., Jenei, C., **Papp, T. B.**, Urbancsek, R., Kolozsvári, R., Rácz, Á., Ráduly, A. P., Veisz, R., Csanádi, Z.: Three-dimensional transesophageal echocardiographic evaluation of pulmonary vein anatomy prior to cryoablation: validation with cardiac CT scan.
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5. Urbancsek, R., Csanádi, Z., Forgács, I. N., **Papp, T. B.**, Boczán, J., Barta, J., Jenei, C., Nagy, L. T., Rudas, L.: The Feasibility of Baroreflex Sensitivity Measurements in Heart Failure Subjects: the Role of Slow-patterned Breathing.
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6. Urbancsek, R., Forgács, I. N., **Papp, T. B.**, Boczán, J., Barta, J., Édes, I., Csanádi, Z., Rudas, L.: Cardiovagalis és szimpatikus artériás baroreflex szabályozásának vizsgálata szívelégtelenségben.
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DOI: http://dx.doi.org/10.1556/650.2021.31962
IF: 0.707

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