



Original Research

Mortality on DOACs Versus on Vitamin K Antagonists in Atrial Fibrillation: Analysis of the Hungarian Health Insurance Fund Database

Tímea Papp, MD¹; Zoltán Kiss, MD²; György Roksztin, MD³; Ibolya Fábián, MSc^{3,4}; László Márk, PhD, MD⁵; Zsuzsa Bagoly, PhD, MD⁶; Dávid Becker, Prof PhD⁷; Béla Merkely, Prof PhD⁷; Dániel Aradi, PhD, MD^{7,8}; Csaba András Dézsi, Prof PhD^{9,10}; Zoltán Járai, Prof PhD¹¹; and Zoltán Csanádi, Prof PhD¹

¹Department of Cardiology, Faculty of Medicine Debrecen, University of Debrecen, Debrecen, Hungary; ²Second Department of Medicine and Nephrology-Diabetes Center, Faculty of Medicine Pécs, University of Pécs, Pécs, Hungary; ³RxTarget Ltd, Szolnok, Hungary; ⁴University of Veterinary Medicine, Budapest, Hungary; ⁵Department of Cardiology, Békés County Central Hospital Pándy Kálmán Branch, Gyula, Hungary; ⁶Division of Clinical Laboratory Sciences, Department of Laboratory Medicine, Faculty of Medicine Debrecen, University of Debrecen, Debrecen, Hungary; ⁷Heart and Vascular Centre, Faculty of Medicine, Semmelweis University, Budapest, Hungary; ⁸Heart Centre Balatonfüred, Balatonfüred, Hungary; ⁹Faculty of Health and Sport Sciences, Széchenyi István University, Győr, Hungary; ¹⁰Department of Cardiology, Petz Aladár University Teaching Hospital, Győr, Hungary; and ¹¹Department of Cardiology, St. Imre University Teaching Hospital, Budapest, Hungary

ABSTRACT

Purpose: Limited real-world data are available on the survival of patients treated with vitamin K antagonists (VKAs) versus with direct oral anticoagulants (DOACs) for nonvalvular atrial fibrillation (AF). In this nationwide registry, we analyzed the mortality risk of patients with nonvalvular AF taking DOACs versus VKAs, with a special attention to the early treatment period.

Methods: The Hungarian National Health Insurance Fund (NHIF) database was searched to identify patients treated with VKA or DOAC as a thromboembolic prophylaxis for nonvalvular AF between 2011 and 2016. The overall and the early (0–3, 4–6, and 7–12 months) mortality risks with the 2 types of anticoagulation were compared. A total of 144,394 patients with AF treated with either a VKA (n = 129,925) or a DOAC (n = 14,469) were enrolled.

Findings: A 28% improvement in 3-year survival with DOAC treatment compared with VKA treatment

was shown. Mortality reduction with DOACs was consistent across different subgroups. However, younger patients (30–59 years old) initiated on DOAC therapy had the greatest RRR (53%) in mortality. Furthermore, DOAC treatment also yielded a benefit of greater magnitude (HR = 0.55; 95% CI, 0.40–0.77, $P = 0.001$) in the lower (0–1) CHA₂DS₂-VASc score segment and in those with fewer (0–1) bleeding risk factors (HR = 0.50, CI 0.34–0.73, $P = 0.001$). The RRR in mortality with DOACs was 33% within the first 3 months, and 6% in the second year.

Implications: Thromboembolic prophylaxis with DOACs in this study yielded significantly lower mortality compared with VKA treatment in patients with nonvalvular AF. The largest benefit was shown

Accepted for publication March 10, 2023

<https://doi.org/10.1016/j.clinthera.2023.03.008>

0149-2918/\$ - see front matter

© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

in the early period after treatment initiation, as well as in younger patients, those with a lower CHA₂DS₂-VASc score, and those with fewer bleeding risk factors. (*Clin Ther.* 2023;45:333–346.) © 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Key words: atrial fibrillation, direct oral anticoagulant, mortality risk reduction, thromboembolism, vitamin K antagonist.

INTRODUCTION

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice, with an estimated prevalence of 3% in the general population worldwide^{1,2} and between 2.37% and 2.67% in Hungary.³ The incidence and prevalence of AF display a constantly rising tendency,^{4,5} with an expected 2.5-fold increase in the next 3 decades, as a result of the aging population and more efficient diagnostic and treatment options.^{6,7} Due to a set of associated comorbidities and the significantly increased mortality,⁸ AF poses an enormous health care burden.⁹ 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 with either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs).^{10,11} Although VKAs have been widely used for anticoagulation in AF, DOACs are recommended based on the latest guidelines,¹² considering the several shortcomings of VKA therapy. These include a narrow therapeutic range, the frequent need for international normalized ratio (INR) monitoring and dose adjustments, and numerous food and drug interactions.¹³ In addition, Azoulay et al¹⁴ 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 values 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.¹⁵ However,

limited data exist regarding hard end points on short- versus long-term therapy with different oral anticoagulants (OACs).¹⁶ Herein, we studied the all-cause mortality in patients diagnosed with nonvalvular AF in Hungary between 2011 and 2016, treated with either a VKA or a DOAC. We also analyzed the mortality risk with the 2 treatment options early after the initiation of therapy versus long term.

PATIENTS AND METHODS

Patient Population

This nationwide, retrospective, longitudinal study included patients with AF from January 1, 2011, through December 31, 2016, using the Hungarian National Health Insurance Fund (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, 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 (Figure 1).

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

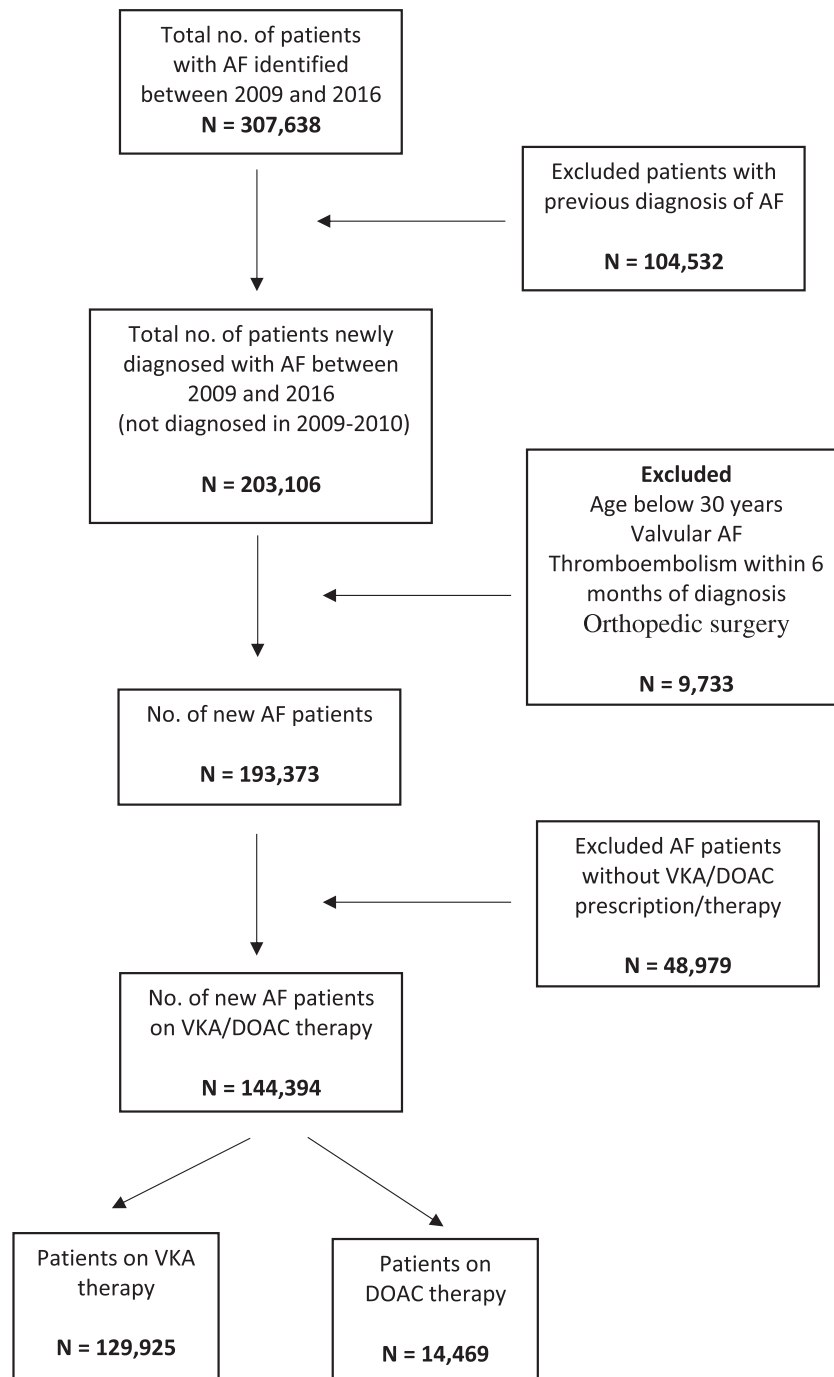


Figure 1. Patient population flowchart. AF = atrial fibrillation; DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

Table I. Thrombotic risk profile characterization.

CHA ₂ DS ₂ -VASc score		ICD/ATC/NOMESCO Codes	Comment	Points
C	Congestive heart failure	ICDs: I50 and I42, I110, J81	Two incidences of any of these codes	1
H	Hypertension	ICDs: I10 Antihypertensive drugs, ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52	Occurrence of ICD together with fulfillment of a hypertension drug with at least twice redeem of an ATC drug within a period of 30 to 365 days	1
A	Age		Age 65–74 years	1
			≥75 years	2
D	Diabetes mellitus	ICDs: E10, E11, or E14; ATC: A10	Two incidences of T2DM ICDs or two prescriptions of antidiabetic treatment	1
S	Stroke/TIA/previous thromboembolism	ICDs: I61, I6290, I63, I64, I74; ICHI codes for CT/MRI: 34410, 34411, 34412, 34490, 34914 and 34915, I6310, I6340, I7400, I7410, I7420, I7430, I7440, I7450, I7480, I7490	Two incidences of any of these codes	2
VA	Vascular disease (peripheral artery disease, myocardial infarction)	ICDs: I21, I22, I700, I701, I702, I703, I704, I705, I706, I707, I708, I709, I2500, I2510, I7039, I2300, I2310, I2320, I2330, I2340, I2350, I2360, I2370, I2380, I2390, I701, I702, I703, I704, I705, I706, I707, I708, I709, I7039, I2100, I2110, I2120, I2130, I2140, I2190, I2200, I2210, I2280, I2290, I2300, I2310, I2320, I2330, I2340, I2350, I2360, I2370, I2380, I2390	Two incidences of any of these codes	1
Sc	Sex category		Male	0
			Female	1

ATC = Anatomical Therapeutic Chemical; CT = computed tomography; ICD = International Classification of Diseases; MRI = magnetic resonance imaging; NOMESCO = Nordic Medico-Statistical Committee; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; ICHI = International Classification of Health Interventions.

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

CHA₂DS₂-VASc score (Table I). 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 (Table II).

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 30, 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, CHA₂DS₂-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).

Statistical Analysis

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, 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. The analysis was performed by using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Between January 1, 2011, and December 31, 2016, a total of 144,394 patients with AF meeting the study inclusion criteria were identified (Figure 1). 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 (Table III). The mean age of the AF population in the DOAC arm was 73.5 (11.31) years, the mean CHA₂DS₂-VASc score was 4 (1.78), 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%; $P < 0.0001$).

36 Months' Survival With DOAC Therapy Versus VKA Therapy

The survival rate 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 (HR, 0.72; 95% CI, 0.69–0.75; $P < 0.001$) (Figure 2). If the $RRR = (CER - EER)/CER$ formula is used to calculate the RRR, where CER is the event rate in the control group (VKA treatment), and EER is the event rate in the experiment group (DOAC treatment), the raw value of the RRR is 15.3%. 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, 0.67–0.77; $P < 0.001$]; 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 (Figure 3). 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 CHA₂DS₂-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 CHA₂DS₂-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%).

Table II. Bleeding risk profile characterization.

Bleeding Risk Factors	ICD/ATC/NOMESCO Codes	Comment	Points
Hypertension	ICDs: I10 Antihypertensive drugs, ATC: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DA, C09DB, C09XA02, C09XA52	Occurrence of ICD together with fulfillment of a hypertension drug with at least twice redeem of an ATC drug within a period of 30 to 365 days	1
Abnormal liver/renal function	ICDs (ICD-10): B15, B16, B17, B18, B19, C22, K70, K71, K72, K73, K74, K75, K76, K77, Z944, I982, D684C, Q618A ICDs (ICD-10): N02, N03, N04, N05, N06, N07, N08, N11, N12, N14, N18, N19, N26, N158, N159, N160, N162, N163, N164, N168, Q612, Q613, Q615, Q619, E102, E112, E132, E142, I120, M300, M313, M319, M321B	One occurrence of defined ICDs in out and inpatient (as primary or secondary discharge code) records of liver chronic liver disease, cirrhosis, and hepatitis One occurrence of defined ICDs in outpatient and inpatient (as primary or secondary discharge code) records of chronic glomerulonephritis, chronic tubulointerstitial nephropathy, diabetic, and hypertensive nephropathy among others	1
Stroke history	ICDs: I61, I6290, I63, I64, I74; ICHI codes for CT/MRI: 34410, 34411, 34412, 34490, 34914 and 34915, I6310, I6340, I7400, I7410, I7420, I7430, I7440, I7450, I7480, I7490	Two incidences of any of these codes	1
Bleeding history	ICDs: D62, I60, I61, I62, R31, R04, D500, H313, H356, H431, H450, I312, I850, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K625, K661, K920, K921, K922, S064, S065, S066, J942, K228F, K298A, K638B, K638C, K838F, K868G, I864A, H052A, S368D, G951A, I6000 I6010 I6020 I6030 I6040 I6050 I6060 I6070 6080 I6090, I8500, K2500, K2520, K2540, K2560, K2600, K2620, K2640, K2660, K2700, K2720, K2740, K2760, K2800, K2820, K2840, K2860, K2900, K6250, K9220	● One occurrence of following bleeding ICD only in inpatient (as primary or secondary discharge code) records: intracranial bleeding, major gastrointestinal bleeding, respiratory, renal/urinary tract, ocular, retroperitoneal or pericardial bleeding, and bleeding attributed to anemia ● Only bleeding episodes requiring hospitalization were used ● Intracranial bleeding is defined as intracerebral hemorrhage, nontraumatic/traumatic subarachnoid hemorrhage, traumatic subdural hemorrhage, and traumatic epidural hemorrhage	1

(continued on next page)

Table II. (continued)

Bleeding Risk Factors	ICD/ATC/NOMESCO Codes	Comment	Points
Labile INR	Not included for score calculation as data on INR levels were not available		
Elderly		Age ≥ 75 years	1
Drugs/alcohol abuse	ICDs: F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292, L278A, ATC: N07BB, Acetylsalicylic acid: ATC: B01AC06, N02BA01, NSAID: ATC: M01A (excludes glucosamine M01AX05)	One occurrence of defined ICDs in out and inpatient (as primary or secondary discharge code) records of alcohol-related diagnosis codes or at least 1 dispensed prescription of an alcohol antagonist drug used to treat chronic alcoholism	1

ATC = Anatomical Therapeutic Chemical; CT = computed tomography; ICD = International Classification of Diseases; INR = international normalized ratio; MRI = magnetic resonance imaging; NOMESCO = Nordic Medico-Statistical Committee; ICHI = International Classification of Health Interventions, NSAID = Non-steroidal anti-inflammatory drug.

Table III. Baseline patient characteristics.

	On DOAC	On VKA	<i>P</i>
Age (Mean $\pm$ SD)	73.5 $\pm$ 11.31	71.7 $\pm$ 10.67	<0.0001
Female (%)	51.01	50.01	0.1568
CHA ₂ DS ₂ -VASc score (Mean $\pm$ SD)	4 $\pm$ 1.78	3.7 $\pm$ 1.7	<0.0001
Bleeding risk factors (Mean $\pm$ SD)	3.2 $\pm$ 1.2	3 $\pm$ 1.16	<0.0001
Total	14469	129925	

DOAC = direct oral anticoagulant; VKA = vitamin K antagonist.

Time-Dependent Differences of Mortality Risk

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 (Figure 4). 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 (Figure 5). 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, 0.22–0.45; $P < 0.001$) in the first 3 months, and an RRR of 33% (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.

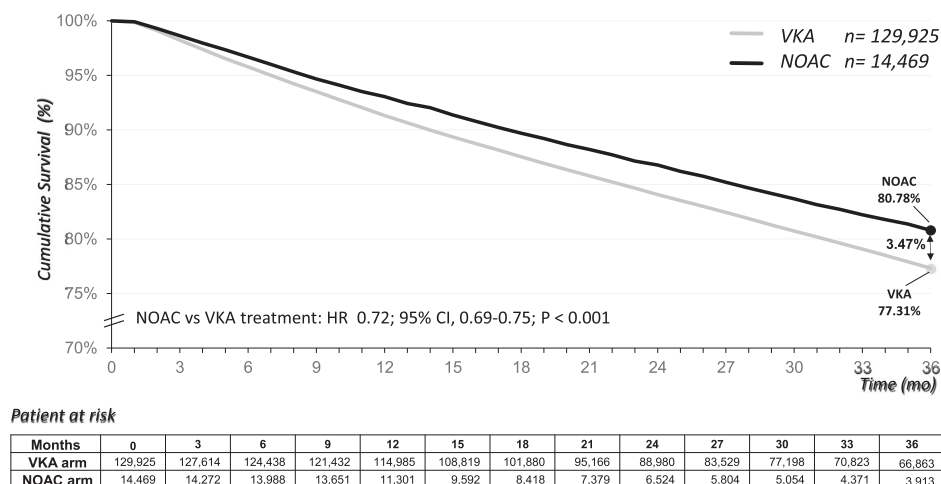


Figure 2. Cumulative 36 months' survival of patients with atrial fibrillation treated with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs). HR = hazard ratio.

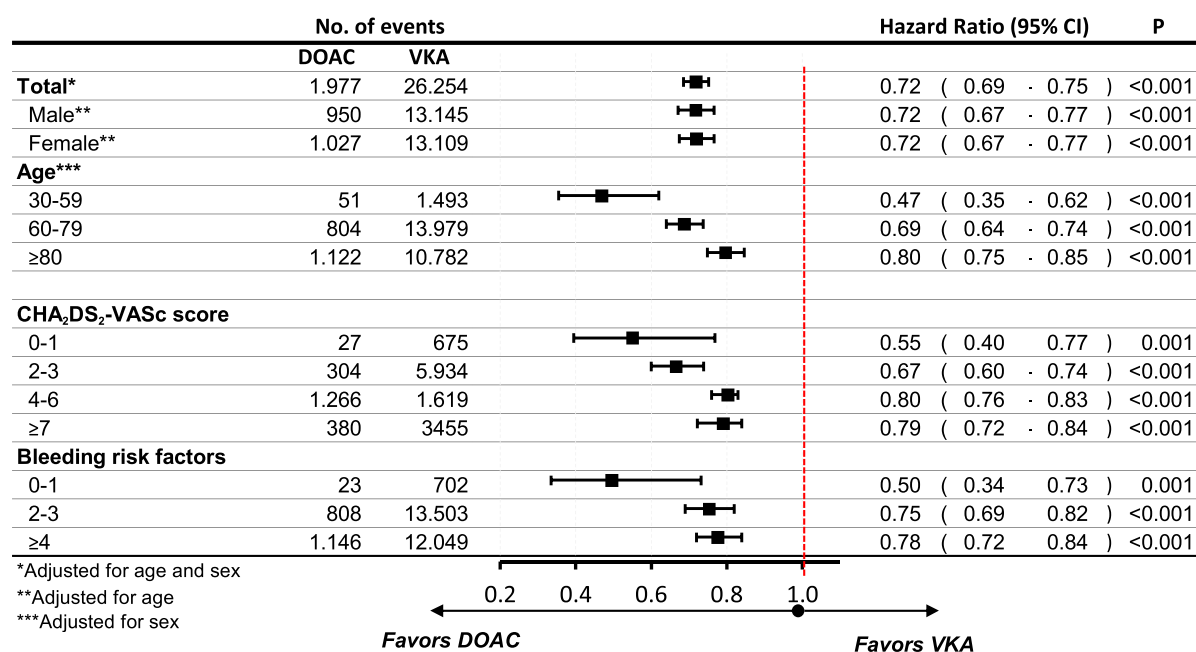


Figure 3. Adjusted 3-year mortality-free survival of patients with atrial fibrillation receiving direct oral anticoagulant (DOAC) treatment compared with vitamin K antagonist (VKA) therapy, according to age, sex, CHA₂DS₂-VASc score, and bleeding risk factors. HR = hazard ratio.

DISCUSSION

A meta-analysis of the 4 pivotal clinical trials¹¹ 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. It is well known that studies based on real-world practice might provide somewhat different conclusions compared with the tightly controlled setting of clinical trials. We analyzed the data of >140,000 patients from the Hungarian insurance

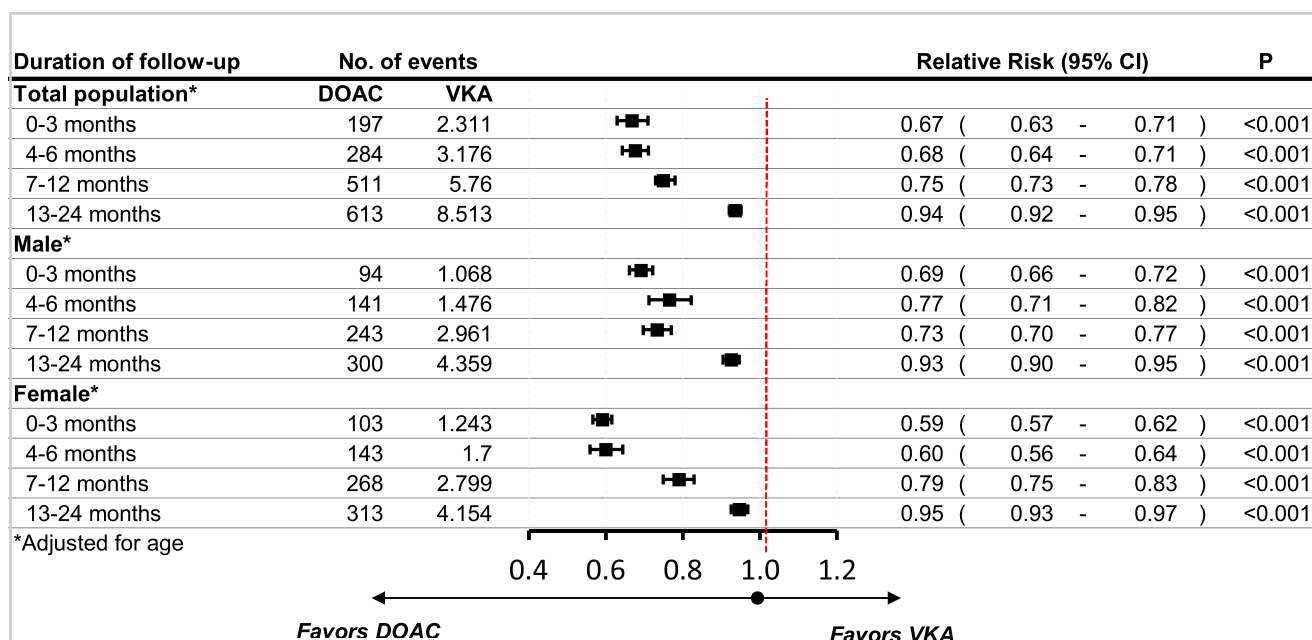


Figure 4. Adjusted risk of mortality of investigated population with atrial fibrillation treated with direct oral anticoagulants (DOACs) compared with vitamin K antagonist (VKA) treatment according to the duration of follow-up and sex.

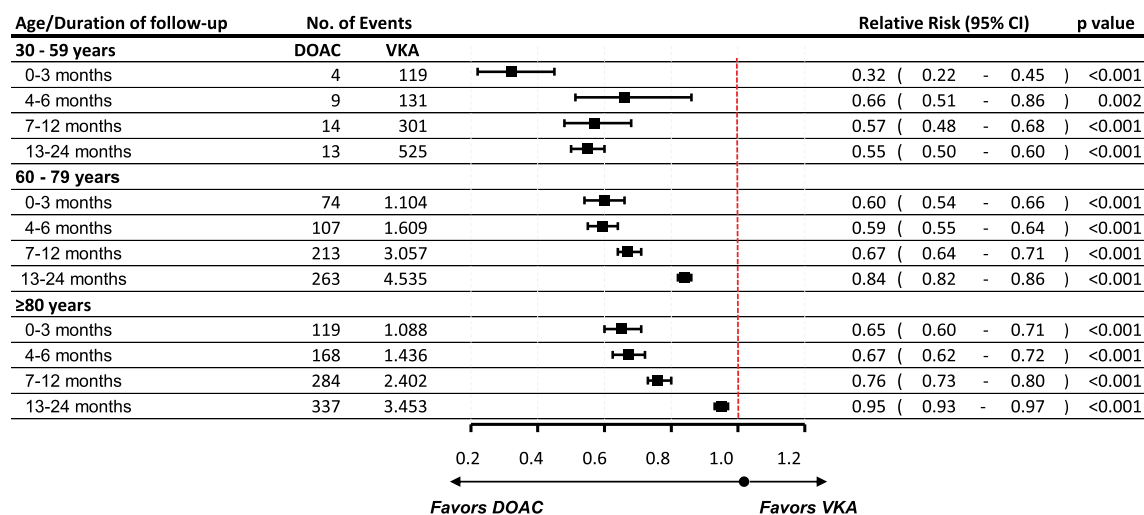


Figure 5. Adjusted mortality risk of the investigated patient population treated with direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs) according to the duration of follow-up and age range.

database and found a 3-year mortality rate of 19.22% for patients taking DOACs and 22.69% in those receiving VKA therapy, which corresponds to a significant 28% reduction in all-cause mortality

(Figure 2). These results are similar to the 33% RRR reported in a meta-analysis of 21 Asian registries.¹⁷ An even more marked 49% RRR was reported with DOACs in Taiwanese patients aged >65 years.¹⁸ Data

from the Danish National registry¹⁹ showed a 35% and 37% RRR on annual mortality with apixaban and dabigatran, respectively, but no significant difference with rivaroxaban. Registry data from Sweden indicated an 11% RRR in favor of DOAC therapy.²⁰ However, no mortality benefit was found in another analysis that included patients with time in therapeutic range (TTR) >70% on warfarin therapy.²¹

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.²² 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.²³ Wide variations in TTR values can be observed even in randomized trials, including a post hoc analysis of the ROCKET-AF study (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) depending not only on patient characteristics but also on geographical regions.²⁴ This likely represents socioeconomic differences and the attitude of patients regarding following strict recommendations, which require significant long-term compromise on a daily basis with no apparent, perceivable effect on their health. Indeed, the optimal value of TTR $\geq 70\%$ is difficult to achieve in clinical practice. Cotté et al²⁵ 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 al²⁴ 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.²⁶

The compliance and persistence of Hungarian patients are poor as far as statin therapy is concerned.²⁷ In a study based on the prescription database of the Hungarian NHIF,²⁸ 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 (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients With Atrial Fibrillation).²⁹ These differences might be of larger magnitude in some geographical regions, resulting in an even more significant advantage with the use of DOACs.

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. This could likely be attributed to the reluctance of many Hungarian patients to take any OAC medication long term, which thereby results in the inappropriate practice of restricting initiation of antithrombotic therapy mostly to those with a very high CHA₂DS₂-VASc-score. 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 CHA₂DS₂-VASc-scores, representing a more favorable thromboembolic and bleeding risk profile (Figure 3). 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.^{27,30} Singer et al²⁴ reported a TTR at 33.3% among patients with a CHA₂DS₂-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 trials³¹ 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 (Figures 4 and 5) 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.”³² 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,³³ 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.²⁹

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.^{14,34,35} 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.^{36,37} 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: the overall RRR of all-cause mortality in the DOAC arm was 33% (41% in female patients and 31% in male patients) in the first 3 months, whereas it was 6% (5% in female patients and 7% in male patients) throughout the second year (Figure 4). In addition, the increased benefit of DOAC treatment early after therapy initiation was even more pronounced in patients aged <60 years (Figure 5), also in support of the compliance problems in younger patients.²⁷ Indeed, the relative difference in the short- versus the long-term term benefit of DOACs was greater in our study than what has been reported in the few available studies.¹⁹

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; RRR in female patients treated with DOAC was 40%, whereas in male patients this value ranged between 23% and 31% during the first 6 months of the therapy. Female sex by itself is a known risk factor for stroke and consequently for a higher all-cause mortality in case of AF, due to a generally older age at AF diagnosis, sex-related differences in cardiovascular remodeling, and hormone level fluctuations during the menstrual cycle, hormone therapy, pregnancy, or menopause.^{38,39} In an editorial comment, Renda and De Caterina⁴⁰ attributed the higher early mortality of female patients treated with VKA to the fluctuations in anticoagulation control at the beginning of therapy, a potential risk eliminated with DOAC treatment. The advantage from DOAC therapy was also reported by Law et al⁴¹: DOAC treatment compared with VKA treatment resulted in a 45% reduction in all-cause mortality in women but not in men.

The current study had several strengths. In this nationwide registry of a nonvalvular AF population, we were able to provide a detailed evaluation of mortality risk comparing VKA and DOAC treatment in patients with variable thromboembolic and bleeding risk at different time points after therapy initiation. The sample size of the patient groups, the high number of events, and the long follow-up provided sufficient power for the analysis, and the observations are relevant to routine care practice.

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. Another limitation is that the adherence rate was not estimated by tracking the filling of prescriptions and dispensation records.

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 CHA₂DS₂-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.

CONCLUSIONS

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. 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. These data support the use of DOACs in preference to VKA in the whole spectrum of patients with nonvalvular AF, including younger individuals with fewer comorbidities. Different magnitude of benefit can be expected from DOAC therapy compared with VKA prophylaxis in patients with AF based on the difference in TTR values specific to a geographical region.

DECLARATION OF INTEREST

Dr Roksztin and Ms Fábíán were employed by RxTarget Ltd. Their contribution to this study analysis was financially compensated by the Hungarian Society of Cardiology. Dr Becker reports personal fees from Novo Nordisk, Richter Gedeon Nyrt, and TEVA. Dr Aradi reports lecture fees from Bayer AG, Pfizer, Boehringer Ingelheim, and MSD Pharma. Dr Merkely reports grants or contracts from Medtronic and Boston Scientific; and personal fees from Biotronik and Abbott. Dr Járái reports support for attending meetings from Egis and Pfizer; advisory board membership at Bayer, Berlin Chemie, KRKA, Novartis, Novo Nordisk, Pfizer, Sanofi, and TEVA; and board membership at the Hungarian Society of Hypertension, Hungarian Society of Cardiology, Hungarian Society of Angiology and Vascular Surgery, and Hungarian Society

of Experimental and Clinical Pharmacology. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

ACKNOWLEDGMENTS

This study was financially supported by the GINOP-2.3.2-15-2016-00043 project (European Union and European Regional Development Fund) and by the Hungarian Society of Cardiology.

The authors thank the NHIF for providing a comprehensive data set for this analysis.

Drs Papp, Csanádi, Kiss, and Roksztin provided the idea for the study and were involved in the interpretation of the data and discussion of the results. Drs Papp, Kiss, and Csanádi interpreted the data and wrote the paper. Dr Roksztin and Ms Fábíán conducted the statistical analysis. Drs Márk, Bagoly, Becker, Merkely, Aradi, Dézsi, and Járái provided critical feedback and contributed to the research, analysis, and preparation of the manuscript.

REFERENCES

1. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893–2962.
2. Björck S, Palaszewski B, Friberg L, et al. Atrial fibrillation, stroke risk, and warfarin therapy revisited: a population-based study. *Stroke*. 2013;44:3103–3108.
3. Tomcsányi J, Bózsik B, Roksztin Gy, et al. The prevalence of atrial fibrillation in Hungary. *Orv Hetil*. 2012;153:339–342.
4. Schnabel RB, Yin X, Gona P, et al. 50 Year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162.
5. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837–847.
6. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. National implication for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA*. 2001;285:2370–2375.
7. Morin DP, Bernard ML, Madias C, et al. The state of the art: atrial fibrillation epidemiology, prevention, and treatment. *Mayo Clin Proc*. 2016;12:1778–1810.
8. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death. The Framingham Heart Study. *Circulation*. 1998;98:946–952.

9. Wu EQ, Birnbaum HG, Mareva M, et al. Economic burden and co-morbidities of atrial fibrillation in a privately insured population. *Curr Med Res Opin.* 2005;21:1693–1699.
10. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA.* 2003;290:2685–2692.
11. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955–962.
12. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: a Report of the ACC/AHA Task Force on Clinical Practice Guidelines and the HRS in Collaboration with the STC. *Circulation.* 2019;140:e125–e151.
13. Datar M, Crivera C, Rozjabek H, et al. Comparison of real-world outcomes in patients with nonvalvular atrial fibrillation treated with direct oral anticoagulant agents or warfarin. *Am J Health Syst Pharm.* 2019;76:275–286.
14. Azoulay L, Dell’Aniello S, Simon TA, et al. Initiation of warfarin in patient with atrial fibrillation: early effects on ischaemic strokes. *Eur Heart J.* 2014;35:1881–1887.
15. Ingrasciotta Y, Fontana A, Mancuso A, et al. Comparison of direct oral anticoagulant use for the treatment of non-valvular atrial fibrillation in pivotal clinical trials vs. the real-world setting: a population-based study from southern Italy. *Pharmaceuticals.* 2021;14:290.
16. Forslund T, Wettermark B, Andersen M, et al. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. *Europace.* 2018;20:420–428.
17. Xue Z, Zhang H. Non-vitamin K antagonist oral anticoagulants versus warfarin in Asians with atrial fibrillation. Meta-analysis of randomized trials and real-world studies. *Stroke.* 2019;50:2819–2828.
18. Chao TF, Chiang CE, Liao JN, et al. Comparing the effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in the elderly Asian patients with atrial fibrillation: a nationwide cohort study. *Chest.* 2020;157:1266–1277.
19. Larsen TB, Skjoth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. *BMJ.* 2016;353:i3189.
20. Friberg L, Oldgren J. Efficacy and safety of non-vitamin K antagonist oral anticoagulants compared with warfarin in patients with atrial fibrillation. *Open Heart.* 2017;4:e000682.
21. Sjalander S, Sjogren V, Renlund H, et al. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thromb Res.* 2018;167:113–118.
22. Lehto M, Niiranen J, Korhonen P, et al. Quality of warfarin therapy and risk of stroke, bleeding, and mortality among patients with atrial fibrillation: results from the nationwide FinWAF Registry. *Pharmacoepidemiol Drug Saf.* 2017;26:657–665.
23. Walraven C, Jennings A, Oake N, et al. Effect of study setting on anticoagulation control. A systematic review and metaregression. *Chest.* 2006;129:1155–1166.
24. Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from ROCKET AF clinical trial. *J Am Heart Assoc.* 2013;2:e000067.
25. Cotté FE, Benhaddi H, Duprat-Lomon I, et al. Vitamin K antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries. *Clin Ther.* 2014;36:1160–1168.
26. Brudasca I. Factors influencing vitamin K antagonist therapy. *RJ Lab Med.* 2015;23:159–168.
27. Kiss Z, Nagy L, Reiber I, et al. Persistence with statin therapy in Hungary. *Med Sci.* 2013;9:409–417.
28. Simonyi G, Paksy A, Várnai R, et al. Real-world adherence to oral anticoagulants in atrial fibrillation. *Orv Hetil.* 2020;161:839–845.
29. Koziele M, Mazurek M, Teutsch C, et al. Persistence with anticoagulation for atrial fibrillation: report from the GLORIA-AF Phase III 1-year follow-up. 2020. *J Clin Med.* 2020;9:1969.
30. Skeppholm M, Friberg L. Adherence to warfarin treatment among patients with atrial fibrillation. *Clin Res Cardiol.* 2014;103:998–1005.
31. Gómez-Outes A, Lagunar-Ruiz J, Terleira-Fernández AI, et al. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol.* 2016;68:2508–2521.
32. Tepper PG, Liu X, Hamilton M, et al. Ischemic stroke in nonvalvular atrial fibrillation at warfarin initiation. Assessment via a large insurance database. *Stroke.* 2017;48:1487–1494.
33. Gallagher AM, Setakis E, Plumb JM, et al. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost.* 2011;106:968–977.
34. Diener HC, Granger CB, Patel MR. Is there a period of liability with initiation of warfarin in patients with atrial fibrillation? *Eur Heart J.* 2014;35:1834–1835.

35. Kim Y, Bang OY. Paradoxical procoagulant effect of early doses of warfarin: possible role of non-vitamin K oral anticoagulant in patients with atrial fibrillation-related stroke. *J Stroke*. 2015;17:216–218.
36. Tang EOYL, Lai CSM, Lee KKC, et al. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother*. 2003;37:34–39.
37. Mekaj YH, Mekaj AY, Duci SB, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag*. 2015;11:967–977.
38. Cove CL, Albert CM, Andreotti F, et al. Female sex as an independent risk factor for stroke in atrial fibrillation: possible mechanisms. *Thromb Haemost*. 2013;111:385–391.
39. Wagstaff AJ, Overvad TF, Lip GYH, et al. Is female sex a risk factor for stroke and thromboembolism in patients with atrial fibrillation? A systematic review and meta-analysis. *QJM*. 2014;107:955–967.
40. Renda G, De Caterina R. Sex implications in the response to anticoagulant therapy in atrial fibrillation. *J Am Coll Cardiol*. 2018;72:283–286.
41. Law SWY, Lau WCY, Wong ICK, et al. Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. *J Am Coll Cardiol*. 2018;72:271–282.

* Address correspondence to: Tímea Papp, MD, 22 Móricz Zsigmond St, 4032 Debrecen, Hajdú-Bihar County, Hungary. E-mail: papptimeabianka@gmail.com.