

The Risk of Falling and Consequences of Falling in Patients with Atrial Fibrillation Receiving Different Types of Anticoagulant

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Title: The risk of falling and consequences of falling in patients with atrial fibrillation

Running head: Predictors and consequences of the first fall in patients with atrial fibrillation

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Authors' contributions: IJ, ML and IH conceptualized the study and drafted the manuscript; ML performed statistical analysis; all authors participated in data acquisition and interpretation, critical revision of the manuscript, final approval of submitted version. All authors agree to be accountable for all aspects of the work.

Abstract:

Objective: To investigate predictors of falling requiring visit to emergency department in patients with non-valvular atrial fibrillation (AF) receiving different types of anticoagulants, as well as to investigate clinical consequences of falling in the same population.

Methods: A total of 1,217 patients with non-valvular AF from two institutions were retrospectively evaluated. Physical examination, clinical history and medications profile were obtained from each patient at baseline.

Results: Median age of our cohort was 71 years. There were 52.3% males and 86.1% patients were receiving anticoagulation at the study baseline. Freedom-from-falling 5-year rate was 81.6%. Use/type of anticoagulation was not significantly associated with the risk of falling ($P=0.222$), whereas higher Morse-Fall-Scale (MFS), CHA₂DS₂-VAS_C and HAS-BLED scores were significantly associated with the higher hazard of the first-fall in univariate analyses. In the multivariate Cox-regression model MFS, older age, osteoporosis, higher HDL-cholesterol, higher diastolic-blood-pressure, use of amiodarone, use of diuretics, and use of short and medium-acting benzodiazepines were identified as mutually independent predictors of the first fall. A total of 93/163 (57%) patients suffered a bone fracture during the fall. Type of anticoagulation significantly affected survival after the first fall ($P<0.001$) with patients inadequately anticoagulated with warfarin experiencing worse and patients receiving apixaban and dabigatran experienced best survival after the first fall.

Conclusion: Older patients with comorbidities, taking amiodarone, diuretics, and short and medium acting benzodiazepines are under highest risk of falling. Type and quality of anticoagulation do not seem to affect the risk of falling but significantly affect survival after the first fall.

Keypoints:

- Older patients with AF and comorbidities, taking amiodarone, diuretics, and short and medium acting benzodiazepines are under highest risk of falling.
- Type and quality of anticoagulation are not associated with the risk of the first fall.
- Type and quality of anticoagulation significantly affect survival after the first fall.

Keywords: atrial fibrillation; elderly; direct oral anticoagulants; DOAC; NOAC; warfarin

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia worldwide with the increasing prevalence with age [1]. Advancing age is associated with the risk of fall and fall-related injuries [2, 3]. AF contributes to that risk by different mechanisms, e.g. by impairing cardiac output resulting in cerebral hypoperfusion and potentially leading to syncope, falls, and fall-related injuries [4, 5] or by increasing a number of drugs a person is taking. A majority of AF patients receive oral anticoagulation therapy (OAT) due to high stroke/systemic embolism risk [6]. The benefits of anticoagulation outweigh the risks in patients with atrial fibrillation who fall [7] and there is no reason, in most situations, for OAT discontinuation after the fall. Current European guidelines recommend direct oral anticoagulants (DOACs) over vitamin K antagonists for patients with AF without contraindications to DOACs [8]. Recent meta-analysis by Malik et al compared DOACs with warfarin in patients >75 years of age and found that apixaban appears to provide the best combination of efficacy and safety in this population [9]. Randomized controlled trials (RCTs) might not be fully representative to real-life patients since for example patients with severe comorbidities are excluded from RCTs and real life AF patients are more frequently female gender, older and have high prevalence of comorbidities [10-12], thus real-life studies can provide more relevant insights into efficacy and safety profile of different drugs. It should also be noted that patients without indication for OAT do exist and are often unjustifiably excluded from real-life AF analyses making this group of patients less well defined regarding different outcomes of interest. Since decision to anticoagulate is not random (but guided by predetermined stroke/systemic embolism risk), exclusion of this subgroup of patients might introduce additional bias. The optimal choice of anticoagulation therapy for patients who are at high risk of falling however has never been studied in a real-life cohort. Thus, aims of our study were to investigate the predictors of the first fall among AF patients in the routine practice, to assess the safety of DOACs (apixaban, dabigatran, and rivaroxaban) and warfarin in the same context and to investigate clinical consequences of falling in this population.

2. Patients and methods

We retrospectively investigated a cohort of 1,217 non valvular AF patients who were admitted in two university hospitals between between January 2013 and December 2018 for evaluation prior to the start of OAT. AF was diagnosed on the basis of the 12-lead ECG on admission and the type of AF was divided into paroxysmal, persistent

and permanent. Clinical data were obtained from the hospital information system and through telephone contact with patients/families. Predetermined stroke risk was assessed using the CHA₂DS₂-VAS_C score [13], predetermined major bleeding risk was assessed using the HAS-BLED score [14]. Predetermined risk of falling was assessed using the Morse Fall Scale (MFS) [15]. Physical examination, transthoracic echocardiography, clinical history and medication profile including the use of intravenous therapies were obtained from each patient before discharge from the hospital. The study complies with the Declaration of Helsinki and it was approved by the Institutional Review Boards.

Normality of distribution of numerical variables was assessed using the Shapiro-Wilk test. All investigated numerical variables had non-normal distribution and were presented as median and interquartile range (IQR). Categorical variables presented as ratio and percentage. Outcome of interest was the first fall and time to first fall was defined as time from study inclusion to first documented fall requiring emergency department visit. Time to event analyses were based on the Kaplan-Meier method [16]. Differences in time to first fall and overall survival after the fall among patients on different type of OAT were analyzed using the log-rank test. Univariate associations with the risk of falling presented in the Table 1 and Table 2 were analyzed using the Cox regression analysis. We focused on parameters relevant for AF assessment and those previously shown to be associated with the risk of falling (MFS and included factors). Only variables with significant univariate associations were considered for multivariate analysis which was performed using the backwards selection process. P values <0.05 were considered statistically significant. All analyses were done using MedCalc statistical software, ver 19.4.0 (MedCalc Software bv, Ostend, Belgium). Data screening prior to final analysis was performed using the custom made MS Excel Workbook [17].

3. Results

3.1. General patients' characteristics and the risk of the first fall

We analyzed a total of 1,217 non-valvular AF patients. Median age was 71 years IQR (62-78). There were 637/1,217 (52.3%) male patients. A total of 1,028/1,217 (84.5%) patients had CHA₂DS₂-VAS_C score ≥ 2 points and 339/1,217 (27.9%) patients had HAS-BLED score ≥ 3 points. Majority of patients [1,048/1217 (86.1%)] received

anticoagulation. Most patients were anticoagulated with warfarin [579/1,217 (47.6%)], followed by dabigatran [42/1,217 (19.9%)], rivaroxaban [117/1,217 (9.6%)] and apixaban [110/1,217 (9%)]. Non-anticoagulated patients were receiving aspirin [133/1,217 (10.9%)] or no active therapy [36/1,217 (3%)] and were kept in the analyses to avoid patient selection bias based on the predetermined thrombotic risk.

Median follow-up of our cohort was 46 months. A total of 163 patients experienced a fall. Median time to first fall was not reached. Risk of the first fall was continuously present during follow-up period with continuously declining time to first fall curve. Freedom-from falling rates were 96.3% at one year, 92.5% at two years, 88.6% at three years, 84.9% at four years and 81.6% at five years of follow-up, respectively (Figure 1A).

3.2. Predetermined risk of falling (Morse Fall Scale)

Median MFS score in an overall cohort was 20 points corresponding to low predetermined fall risk on average. A total of 636/1,217 (52.3%) patients had low fall risk, 414/1,217 (34.0%) had moderate fall risk and 167/1,217 (13.7%) had high fall risk according to the MFS.

With the exception of intravenous therapy, other MFS-included parameters (history of falling, 2 or more diagnoses, ambulatory aid, gait and mental status) showed significant associations with the risk of fall as shown in the Table 1. MFS was significantly associated with the fall risk in our cohort of patients ($P < 0.001$) and was able to well discriminate three subgroups of patients with distinct falling risk as shown in the Figure 1B.

3.3. Other factors prognostic of the risk of falling

In addition to MFS and MFS-included parameters, other patients' characteristics and their relationship with the risk of falling are shown in the Table 1. Other factors univariately significantly associated with the increased hazard of the first fall ($P < 0.05$) were older age, female sex, orthostatic instability, peripheral artery disease, chronic obstructive pulmonary disease, dementia, osteoporosis, thyroid disease, lower height, lower weight, lower estimated glomerular filtration rate, lower hemoglobin, higher total and HDL cholesterol, higher systolic and diastolic arterial blood pressure, higher CHA2DS2-VASC and higher HAS-BLED scores.

Medications profile and their relationship with the risk of falling are shown in the Table 2. Medications-related factors associated with the increased hazard of the first fall were number of drugs taken, number of psychiatric drugs, use of amiodarone, use of ACE inhibitors/ARB, use of diuretics, use of anxiolytics, use of sedatives, and use of short and medium acting benzodiazepines.

Type of anticoagulant therapy was not significantly associated with the risk of falling ($P=0.222$) as shown in the Figure 2A: time to first fall curves associated with particular drugs were mutually overlapping without mutually significant differences ($P>0.05$).

Results of the multivariate Cox regression analysis are shown in Table 3. MFS, older age, osteoporosis, higher HDL cholesterol, higher diastolic blood pressure, use of amiodarone, use of diuretics, and use of short and medium acting benzodiazepines remained mutually independently associated with the higher risk of falling.

3.4. Clinical consequences of falling

Out of 163 first falls, a total of 93 (57%) patients suffered a bone fracture. Developing a fracture was not associated with the type of anticoagulant therapy ($P=0.464$). However, overall survival after the first fall significantly differed among patients receiving different types of anticoagulant therapy ($P<0.001$) as shown in the Figure 2B. There were 5/15 deaths in patients receiving no OAT, 7/33 deaths in patients adequately and 33/63 deaths in patients inadequately anticoagulated with warfarin, 2/29 deaths in patients receiving dabigatran, 3/10 deaths in patients receiving rivaroxaban and 0/13 deaths in patients receiving apixaban. Patients taking apixaban and dabigatran experienced best post-fall survival, whereas those patients that were inadequately anticoagulated with warfarin had poorest prognosis. Although interesting, this information is limited by multiple comparisons and small numbers of patients and events in the subgroups and should be interpreted with caution.

4. Discussion

To the best of our knowledge, our study is first to investigate clinical consequences of falling in non-valvular AF patients. Type of anticoagulation therapy did not seem to affect the risk of falling, however, prognosis of patients who experienced the first fall significantly differed depending on the type and quality of anticoagulation therapy.

Older patients (especially females) with higher number of comorbidities and high thrombotic and bleeding risks (higher CHA₂DS₂-VAS_C and HAS-BLED scores), taking amiodarone, diuretics and short and medium acting benzodiazepines are under highest risk of falling. However, besides higher risk of thrombotic incidents and bleeding as assessed through comorbidities, no other AF related factors seem to significantly affect the fall risk. MFS was able to well discriminate the risk of falling in our cohort of patients and was confirmed as a clinically useful instrument with independent prognostic properties for the first fall.

High number of comorbidities dictate the need for multiple medications which is consequently associated with an increased risk of drug-drug interactions and major adverse events. Polypharmacy, especially taking five or more drugs has already been recognized as a risk factors for falls [18-20]. Our study also supports this finding. Among different drugs, especially amiodarone, diuretics and short and medium acting benzodiazepines are significantly associated with the risk of falling. Risk is highest for patients receiving amiodarone (HR=3.15), followed by sedatives (HR=2.52), diuretics (HR=2.01), medium acting benzodiazepines (HR=2.0), short acting benzodiazepines (HR=1.89), ACE inhibitors/ARB (HR=1.76) and anxiolytics (HR=1.64). Long acting benzodiazepines were not significantly associated with the fall risk, same as antipsychotics, antidepressants, antiepileptics. It is very interesting that beta blockers seem to have protective properties regarding the risk of falling, however their use did not remain significant in the multivariate analysis. Also type and quality of anticoagulation therapy did not affect the risk as we mentioned previously.

Real-life studies comparing efficacy and safety profiles of DOACs and warfarin confirmed greater clinical benefit of DOACs in older patients with a better safety profile for apixaban and dabigatran [6, 21-23]. Our study supports these findings as best post-fall survival rates were associated with apixaban and dabigatran and poorest prognosis was associated with inadequately titrated warfarin dose. Before DOACs entered the market, anticoagulant treatment has generally been underused in the elderly patients with AF, particularly due to the risk of falling and physicians' concerns over bleeding [24]. However, Donze et al [25] reported that patients on oral anticoagulants at high risk of falls did not have a higher risk of major bleeds than patients at low risk of falls indicating that the use of oral anticoagulant therapy may be safe and the risk of falling should not be the reason to deny anticoagulation therapy to elderly patients. Challenges remain to choose an optimal type of anticoagulation. Decisions are influenced by the likelihood of drug-drug interactions with drug of choice, patient related factors like obesity [26], etc. We are not aware of direct mechanisms behind differences in post-fall outcomes observed in our study. However, warfarin

and DOACs are usually prescribed to different target populations [6] and differences in patient profile might be affecting post-fall prognosis. Availability of specific antidote and quick reversal of anticoagulation might also play a role, especially concerning the fact that 57% patients in our study suffered a bone fracture and might require urgent surgery. Fresh frozen plasma, idarucizumab (a monoclonal antibody directed against dabigatran) and andexanet alfa (a recombinant modified version of human activated factor X directed reversing effects of apixaban or rivaroxaban) are differently available in real-life clinical practices.

It is also worth mentioning that existing evidence is inconsistent, but concerns have been raised about correlation between warfarin and impaired bone quality [27]. Among different DOACs, particularly apixaban has been associated with lowest risk of fractures in comparison to warfarin [28]. Our data do not indicate there is a different fracture risk associated with warfarin or other type of anticoagulant drug. It is evident however, that inadequately titrated warfarin is associated with poorest prognosis after the fall. Increased post-fall mortality associated with inadequate warfarin dosing is in line with observations of reduced survival that can be seen in an overall AF cohorts as well [6]. Given the risk of fall, and especially consequences of the fall in mind, warfarin should be prescribed with a caution or better avoided to patients with high risk of falling that are unable to obtain adequate control of anticoagulation. According to our study, these patients are mostly older females with high number of comorbidities, and although the optimal choice of anticoagulant therapy cannot definitely be answered by our study, we could suggest apixaban or dabigatran as the therapy choice for these patients.

Our study is limited by retrospective design, small number of patients and events in post-fall analyses resulting in loss of statistical power. Large number of presented statistical analyses might result in higher probability of false positive findings. Some patients who fell might be missed due to visiting another hospital but since all families and patients were contacted by telephone with direct assessment of the history of falling this type of bias should be minimized. Also, specificities of our health-care system regarding availability/reimbursement of DOACs might consequently result in patient selection bias associated with specific drug types. Nevertheless, these do not reflect on the risk of falling. It should be emphasized that no causal relationship can be determined from our data due to the retrospective nature of our study (for example use of different medications can be the cause and the consequence of higher falling risk which cannot be judged from our data due to the study design limitations). Also, we could not compare our post-fall cohort with other types of trauma patients as these data were not available.

In conclusion, our real-life findings reveal that post-fall prognosis differs among AF patients anticoagulated with different drugs. Older patients with AF and comorbidities, taking amiodarone, diuretics, and short and medium acting benzodiazepines are under highest risk of falling, and special concerns should be taken in this vulnerable population.

5. Acknowledgements: none

6. References:

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014 Feb 25;129(8):837-47.
2. Torstensson M, Hansen AH, Leth-Møller K, Jørgensen TS, Sahlberg M, Andersson C, et al. Danish register-based study on the association between specific cardiovascular drugs and fragility fractures. *BMJ open*. 2015 Dec 29;5(12):e009522.
3. Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *Journal of the American Geriatrics Society*. 2011 Jan;59(1):148-57.
4. Jansen S, Frewen J, Finucane C, de Rooij SE, van der Velde N, Kenny RA. AF is associated with self-reported syncope and falls in a general population cohort. *Age and ageing*. 2015 Jul;44(4):598-603.
5. Hung C-Y, Wu T-J, Wang K-Y, Huang J-L, Loh E-W, Chen Y-M, et al. Falls and Atrial Fibrillation in Elderly Patients. *Acta Cardiologica Sinica*. 2013;29(5):436-43.
6. Jurin I, Lucijanac M, Sakic Z, Hulak Karlak V, Atic A, Maglicic A, et al. Patterns of anticoagulation therapy in atrial fibrillation: results from a large real-life single-center registry. *Croatian medical journal*. 2020 Oct 31;61(5):440-9.
7. Garwood CL, Corbett TL. Use of anticoagulation in elderly patients with atrial fibrillation who are at risk for falls. *The Annals of pharmacotherapy*. 2008 Apr;42(4):523-32.
8. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2016 Nov;50(5):e1-e88.
9. Malik AH, Yandrapalli S, Aronow WS, Panza JA, Cooper HA. Meta-Analysis of Direct-Acting Oral Anticoagulants Compared With Warfarin in Patients >75 Years of Age. *The American journal of cardiology*. 2019 Jun 15;123(12):2051-7.
10. Savarese G, Sartipy U, Friberg L, Dahlström U, Lund LH. Reasons for and consequences of oral anticoagulant underuse in atrial fibrillation with heart failure. *Heart*. 2018 Jul;104(13):1093-100.
11. Durham TA, Hassmiller Lich K, Viera AJ, Fine JP, Mukherjee J, Weinberger M, et al. Utilization of Standard and Target-Specific Oral Anticoagulants Among Adults in the United Kingdom With Incident Atrial Fibrillation. *The American journal of cardiology*. 2017 Nov 15;120(10):1820-9.
12. Bo M, Sciarillo I, Li Puma F, Badinella Martini M, Falcone Y, Iacovino M, et al. Effects of Oral Anticoagulant Therapy in Medical Inpatients ≥65 Years With Atrial Fibrillation. *The American journal of cardiology*. 2016 Feb 15;117(4):590-5.

13. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010 Feb;137(2):263-72.
14. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010 Nov;138(5):1093-100.
15. Morse J, Morse R, Tylko S. Development of a scale to identify the fall-prone patient. *Can J Aging*. 1989;8:366-7.
16. Lucijanac M, Petroveckii M. Analysis of censored data. *Biochemia medica*. 2012;22(2):151-5.
17. Lucijanac M. Survival analysis in clinical practice: analyze your own data using an Excel workbook. *Croatian medical journal*. 2016 Feb;57(1):77-9.
18. Kojima T, Akishita M, Nakamura T, Nomura K, Ogawa S, Iijima K, et al. Polypharmacy as a risk for fall occurrence in geriatric outpatients. *Geriatrics & gerontology international*. 2012 Jul;12(3):425-30.
19. LaMori JC, Mody SH, Gross HJ, daCosta DiBonaventura M, Patel AA, Schein JR, et al. Burden of comorbidities among patients with atrial fibrillation. *Therapeutic advances in cardiovascular disease*. 2013 Apr;7(2):53-62.
20. Jaspers Focks J, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, et al. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *Bmj*. 2016 Jun 15;353:i2868.
21. Lip GY, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, et al. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. *International journal of clinical practice*. 2016 Sep;70(9):752-63.
22. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and valvular heart disease. *International journal of cardiology*. 2016 Apr 15;209:181-3.
23. Lip GY, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thrombosis and haemostasis*. 2016 Oct 28;116(5):975-86.
24. Sellers MB, Newby LK. Atrial fibrillation, anticoagulation, fall risk, and outcomes in elderly patients. *American heart journal*. 2011 Feb;161(2):241-6.
25. Donzé J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. *The American journal of medicine*. 2012 Aug;125(8):773-8.
26. Lucijanac M, Jurin I, Jurin H, Lucijanac T, Starcevic B, Skelin M, et al. Patients with higher body mass index treated with direct / novel oral anticoagulants (DOAC / NOAC) for atrial fibrillation experience worse clinical outcomes. *International journal of cardiology*. 2020 Feb 15;301:90-5.
27. Namba S, Yamaoka-Tojo M, Kakizaki R, Nemoto T, Fujiyoshi K, Hashikata T, et al. Effects on bone metabolism markers and arterial stiffness by switching to rivaroxaban from warfarin in patients with atrial fibrillation. *Heart and vessels*. 2017 Aug;32(8):977-82.
28. Lutsey PL, Norby FL, Ensrud KE, MacLehose RF, Diem SJ, Chen LY, et al. Association of Anticoagulant Therapy With Risk of Fracture Among Patients With Atrial Fibrillation. *JAMA internal medicine*. 2019 Nov 25;180(2):245-53.

Table 1: Patients' characteristics and their relationship with the risk of falling.

| | Summary | Univariate relationship with the risk of falling /HR with 95% C.I. and P value |
|--------------------------|--------------------|---|
| Age (years) | 71 IQR (62 - 78) | HR=1.05 (1.03-1.07); P<0.001 * |
| Male sex | 637/1,217 (52.3%) | HR=0.5 (0.37-0.69); P<0.001 * |
| Orthostatic instability | 84/1,217 (6.9%) | HR=4.07 (2.69-6.17); P<0.001 * |
| History of falling | 96/1,217 (7.9%) | HR=2.94 (1.94-4.45); P<0.001 * |
| 2 or more diagnoses | 1012/1,217 (83.2%) | HR=3.18 (1.77-5.73); P<0.001 * |
| No ambulatory aid | 975/1,217 (80.1%) | Reference category |
| Crutches/cane/walker | 140/1,217 (11.5%) | HR=1.51; P=0.111 |
| Furniture | 102/1,217 (8.4%) | HR=6.15 (4.32-8.76); P<0.001 * |
| Intravenous therapy | 132/1,217 (10.8%) | HR=1.43; P=0.121 |
| Normal gait | 902/1,217 (74.1%) | Reference category |
| Weak gait | 231/1,217 (19%) | HR=5.63 (4.02-7.89); P<0.001 * |
| Impaired gait | 84/1,217 (6.9%) | HR=7.44 (4.72-11.73); P<0.001 * |
| Mental status – oriented | 1075/1,217 (88.3%) | HR=0.56 (0.37-0.86); P=0.008 * |
| Morse Fall Scale | | - |
| Low risk | 636/1,217 (52.3%) | Reference category |
| Moderate risk | 414/1,217 (34%) | HR=2.11 (1.45-3.09); P<0.001 * |
| High risk | 167/1,217 (13.7%) | HR=5.83 (3.91-8.89); P<0.001 * |
| Hypertension | 962/1,217 (79%) | HR=1.36; P=0.137 |
| Diabetes mellitus | 256/1,216 (21.1%) | HR=1.12; P=0.578 |
| Prior stroke/TIA | 127/1,217 (10.4%) | HR=1.36; P=0.191 |
| Heart failure | 341/1,217 (28%) | HR=1.14; P=0.455 |
| CAD | 204/1,217 (16.8%) | HR=1.01; P=0.968 |
| CVD family history | 289/1,216 (23.8%) | HR=1.14; P=0.490 |
| PAD | 128/1,217 (10.5%) | HR=1.78 (1.25-2.82); P=0.014 * |

| | | |
|------------------------------------|--------------------------|--|
| COPD | 104/1,217 (8.5%) | HR=1.83 (1.16-2.89); P=0.010 * |
| Dementia | 162/1,217 (13.3%) | HR=1.94 (1.31-2.89); P=0.001 * |
| Osteoporosis | 32/1,217 (2.6%) | HR=3.23 (1.65-6.36); P<0.001 * |
| Thyroid disease | 203/1,217 (16.7%) | HR=1.71 (1.21-2.43); P=0.002 * |
| Malignant disease | 130/1,217 (10.7%) | HR=0.61; P=0.114 |
| Smoking | 206/1,217 (16.9%) | HR=0.99; P=0.972 |
| Alcohol use | 134/1,217 (11%) | HR=0.8; P=0.437 |
| Bleeding history | 53/1,217 (4.4%) | HR=1.6; P=0-146 |
| eGFR (ml/min/1.73m ²) | 66 IQR (53.5 - 81.3) | HR=0.98 (0.97-0.99); P<0.001 * |
| eGFR <60 ml/min/1.73m ² | 465/1,217 (38.2%) | HR=1.87 (1.38-2.55); P<0.001 * |
| Height (cm) | 170 IQR (165 - 178) | HR=0.98 (0.98-0.99); P<0.001 * |
| Weight (cm) | 80 IQR (72.75 - 91) | HR=0.98 (0.97-0.99); P=0.003 * |
| BMI (kg/m ²) | 27.7 IQR (25.39 - 30.49) | HR=1.01; P=0.686 |
| BMI <25 kg/m ² | 261/1,216 (21.5%) | Reference category |
| BMI 25-29.9 kg/m ² | 612/1,216 (50.3%) | HR=0.82; P=0.312 |
| BMI 30-34.9 kg/m ² | 252/1,216 (20.7%) | HR=0.82; P=0.394 |
| BMI 35-39.9 kg/m ² | 69/1,216 (5.7%) | HR=1.43; P=0.283 |
| BMI ≥40 kg/m ² | 22/1,216 (1.8%) | HR=0.81; P=0.727 |
| Total cholesterol (mmol/L) | 4.6 IQR (3.7 - 5.5) | HR=1.12 (1.02-1.23); P=0.024 * |
| LDL cholesterol (mmol/L) | 2.8 IQR (2 - 3.5) | HR=1.13; P=0.065 |
| HDL cholesterol (mmol/L) | 1.1 IQR (0.9 - 1.3) | HR=1.12 (1.10-1.33); P<0.001 * |
| Triglycerides (mmol/L) | 1.5 IQR (1.01 - 1.9) | HR=1.09; P=0.247 |
| Hemoglobin (g/L) | 137 IQR (128 - 146) | HR=0.98 (0.97-0.99); P=0.001 * |
| CRP (mg/L) | 4.3 IQR (1.9 - 7.8) | HR=1; P=0.974 |
| Platelets x10 ⁹ /L | 215 IQR (174 - 263) | HR=1.01; P=0.277 |
| WBC x10 ⁹ /L | 7.6 IQR (6.1 - 9.33) | HR=1.01; P=0.151 |
| Systolic BP (mm Hg) | 130 IQR (120 - 140) | HR=1.01 (1.00-1.02); P=0.007 * |

| | | |
|----------------------|---------------------|--|
| Diastolic BP (mm Hg) | 80 IQR (75 - 90) | HR=1.03 (1.01-1.04); P<0.001 * |
| Paroxysmal AF | 559/1,217 (45.9%) | Reference category |
| Persistent AF | 223/1,217 (18.3%) | HR=1.26; P=0.243 |
| Permanent AF | 435/1,217 (35.7%) | HR=0.91; P=0.601 |
| Preserved EF | 870/1,217 (71.5%) | Reference category |
| Mid-range EF | 225/1,217 (18.5%) | HR=1.12; P=0.578 |
| Reduced EF | 122/1,217 (10%) | HR=0.92; P=0.788 |
| CHA2DS2VASC | 3 IQR (2 - 4) | HR=1.27 (1.17-1.39); P<0.001 * |
| CHA2DS2VASC \geq 2 | 1,028/1,217 (84.5%) | HR=2.29 (1.33-3.97); P=0.003 * |
| HAS-BLED | 2 IQR (1 - 3) | HR=1.24 (1.07-1.44); P=0.004 * |
| HAS-BLED \geq 3 | 339/1,217 (27.9%) | HR=1.51 (1.09-2.08); P=0.012 * |

*statistically significant at level P<0.05

Abbreviations: IQR – interquartile range; HR – hazard ratio; 95% C.I. – 95% confidence interval; CAD – coronary artery disease; CVD – cardiovascular disease; PAD – peripheral artery disease; COPD – chronic obstructive pulmonary disease; eGFR – estimated glomerular filtration rate estimated by Cockcroft-Gault method; BMI – body mass index; LDL – low density lipoprotein; HDL high density lipoprotein; CRP - C reactive protein; WBC – white blood cell count; BP – blood pressure; AF – atrial fibrillation; EF – ejection fraction.

Table 2: Medications profile and their relationship with the risk of falling

| | Summary | Univariate relationship with the risk of falling /HR with 95% C.I. and P value |
|-------------------------|-------------------|---|
| Nm of drugs in total | 6 IQR (4 - 8) | HR=1.11 (1.05-1.17); P<0.001 * |
| Nm of psychiatric drugs | 0 IQR (0 - 1) | HR=1.39 (1.19-1.64); P<0.001 * |
| No OAT or Aspirin | 36/1,217 (3%) | - |
| Aspirin only | 133/1,217 (10.9%) | Reference category |

| | | |
|----------------------|-------------------|--|
| Optimal warfarin | 214/1,217 (17.6%) | HR=1.39; P=0.287 |
| Non-optimal warfarin | 365/1,217 (30%) | HR=1.66; P=0.079 |
| Dabigatran | 242/1,217 (19.9%) | HR=1.17; P=0.627 |
| Rivaroxaban | 117/1,217 (9.6%) | HR=0.92; P=0.847 |
| Apixaban | 110/1,217 (9%) | HR=1.05; P=0.902 |
| Aspirin | 192/1,217 (15.8%) | HR=0.69; P=0.132 |
| Amiodarone | 186/1,216 (15.3%) | HR=3.15 (2.29-4.34); P<0.001 * |
| Beta blockers | 938/1,217 (77.1%) | HR=0.39 (0.28-0.53); P<0.001 * |
| ACE inhibitors/ARB | 993/1,217 (81.6%) | HR=1.76 (1.1-1.8); P=0.018 * |
| Diuretics | 777/1,217 (63.8%) | HR=2.01 (1.41-2.88); P<0.001 * |
| Ca channel blockers | 378/1,217 (31.1%) | HR=1.23; P=0.209 |
| Digoxin | 129/1,217 (10.6%) | HR=0.68; P=0.213 |
| Moxonidin | 59/1,217 (4.8%) | HR=0.91; P=0.816 |
| Urapidil | 11/1,217 (0.9%) | HR=1.84; P=0.389 |
| Nitrates | 22/1,217 (1.8%) | HR=0.61; P=0.489 |
| Antipsychotics | 78/1,216 (6.4%) | HR=1.69; P=0.052 |
| Antidepressants | 59/1,217 (4.8%) | HR=0.91; P=0.804 |
| Anxiolytics | 321/1,217 (26.4%) | HR=1.64 (1.19-2.27); P=0.002 * |
| Sedatives | 125/1,217 (10.3%) | HR=2.52 (1.69-3.78); P<0.001 * |
| Antiepileptics | 20/1,217 (1.6%) | HR=0.36; P=0.318 |
| No benzodiazepines | 881/1,217 (72.4%) | Reference category |
| Short acting | 161/1,217 (13.2%) | HR=1.89 (1.28-2.78); P=0.001 * |
| Medium acting | 117/1,217 (9.6%) | HR=2.0 (1.27-3.15); P=0.003 * |
| Long acting | 58/1,217 (4.8%) | HR=1.19; P=0.655 |

*statistically significant at level P<0.05

Abbreviations: IQR – interquartile range; HR – hazard ratio; 95% C.I. – 95% confidence interval; OAT – oral anticoagulation therapy; ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; Ca – calcium.

Table 3: Multivariate Cox regression model investigating mutually independent contribution of univariately significant variables to the risk of the first fall.

| Variable | Multivariate relationship with the risk of falling /HR with 95% C.I. and P value |
|----------------------------------|---|
| MFS Moderate vs Low | HR=2.51 (1.69 - 3.74); P<0.001 * |
| MFS High vs Low | HR=4.66 (2.92 - 7.42); P<0.001 * |
| Age (years) | HR=1.03 (1.01 - 1.05); P=0.001 * |
| Dementia | HR=0.62; P=0.053 |
| Osteoporosis | HR=2.34 (1.17 - 4.66); P=0.016 * |
| Thyroid disease | HR=1.32; P=0.146 |
| HDL cholesterol (mmol/L) | HR=1.25 (1.13 - 1.39); P<0.001 * |
| Hemoglobin (g/L) | HR=0.99; P=0.062 |
| Diastolic blood pressure (mm Hg) | HR=1.02 (1.01 - 1.04); P=0.001 * |
| Amiodarone | HR=2.47 (1.7 - 3.58); P<0.001 * |
| Beta blockers | HR=0.77; P=0.176 |
| Diuretics | HR=1.54 (1.05 - 2.27); P=0.027 * |
| Short acting benzodiazepines | HR=1.61 (1.08 - 2.39); P=0.018 * |
| Medium acting benzodiazepines | HR=1.94 (1.18 - 3.16); P=0.008 * |

*statistically significant at level P<0.05

Abbreviations: HR – hazard ratio; 95% C.I. – 95% confidence interval; MFS – Morse Fall Scale; HDL – high density lipoprotein.

Figure 1: A) Time to first fall curve for the whole cohort and **B)** stratified according to the Morse Fall Scale risk groups.

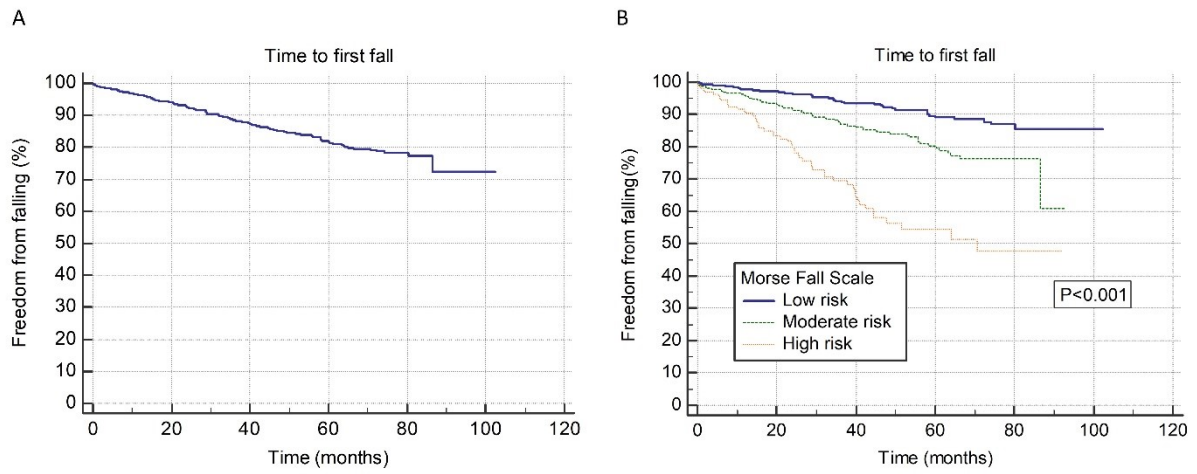


Figure 2: A) Time to first fall curve stratified according to the type of anticoagulation. **B)** Post-fall overall survival stratified by the type of anticoagulation.

