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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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), CHA_2DS_2-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 CHA_2DS_2-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-VASC 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, out 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 CHA_2DS_2-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

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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 Persistent AF Permanent AF	559/1,217 (45.9%) 223/1,217 (18.3%) 435/1,217 (35.7%)	Reference category HR=1.26; P=0.243 HR=0.91; P=0.601
Preserved EF Mid-range EF Reduced EF	870/1,217 (71.5%) 225/1,217 (18.5%) 122/1,217 (10%)	Reference category HR=1.12; P=0.578 HR=0.92; P=0.788
CHA2DS2VASC	3 IQR (2 - 4)	**HR=1.27 (1.17-1.39); P<0.001 ***
CHA2DS2VASC ≥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 ≥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 Aspirin only	36/1,217 (3%) 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.

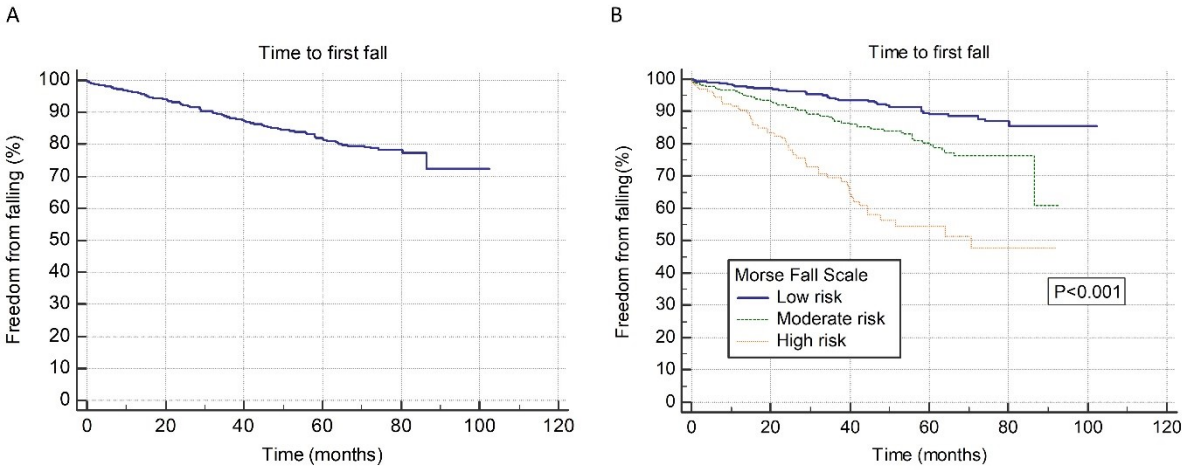

Figure 2: A) Time to first fall curve stratified according to the type of anticoagulation. **B)** Post-fall overall survival stratified by the type of anticoagulation.